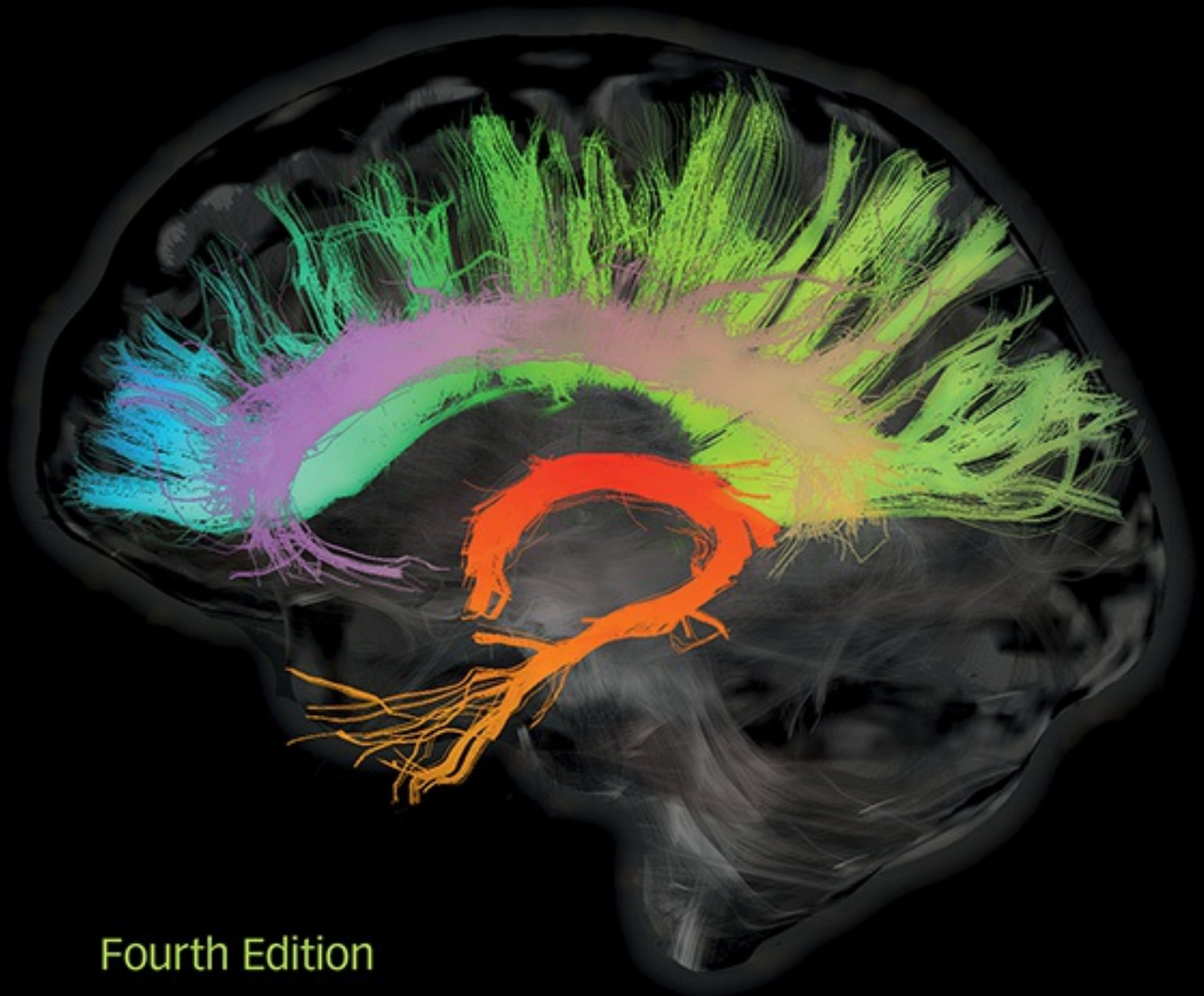


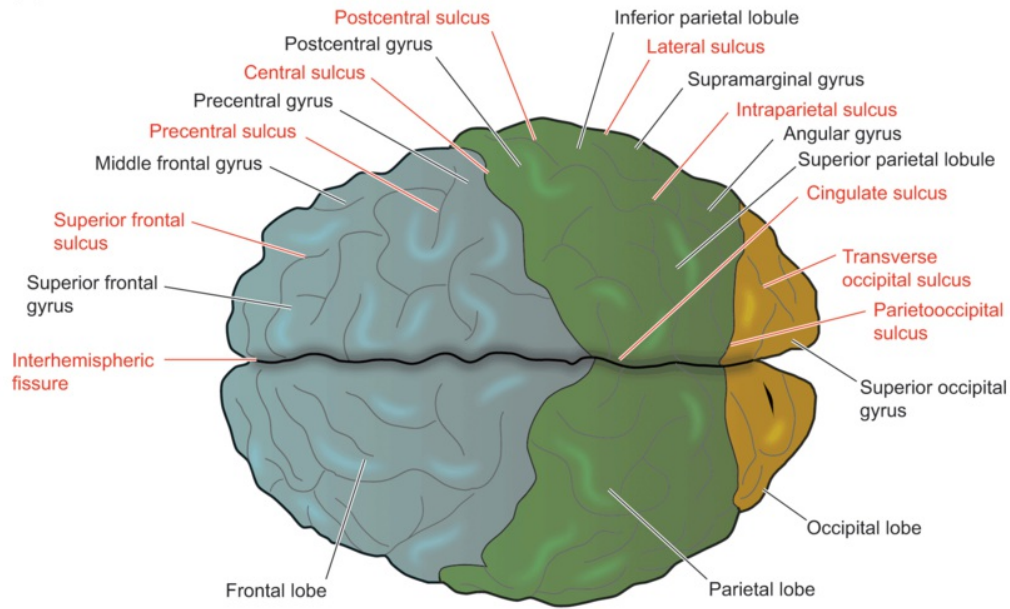
Marie T. Banich and Rebecca J. Compton

COGNITIVE NEUROSCIENCE

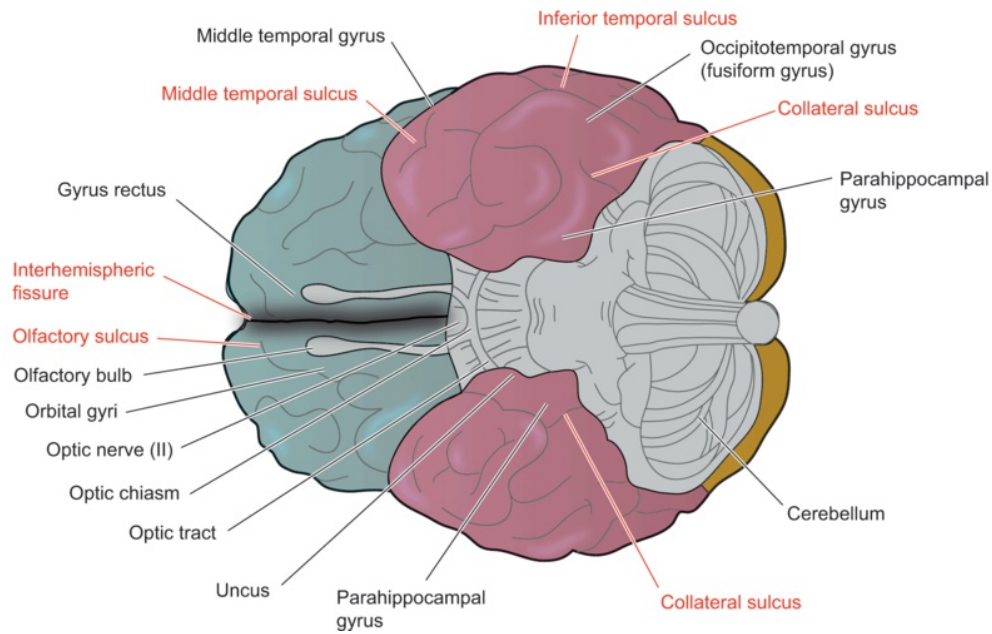


Fourth Edition

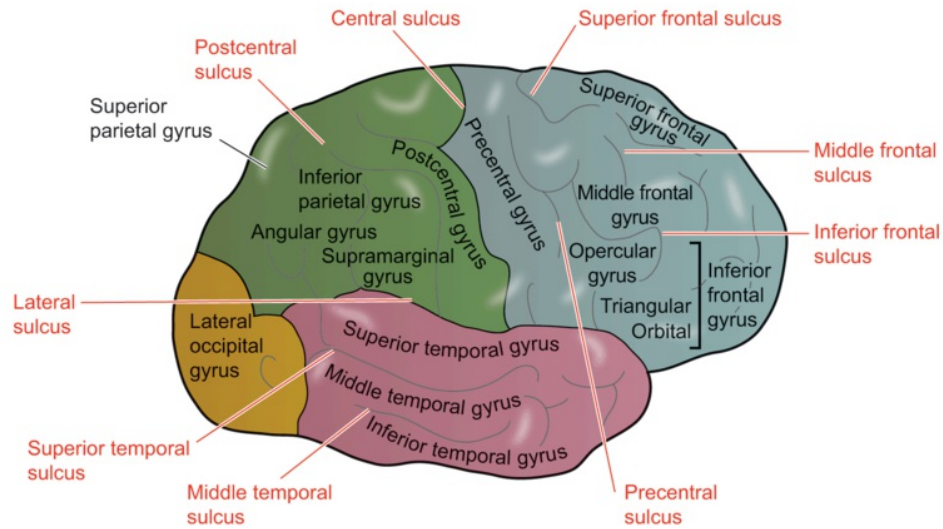
(A) Dorsal View



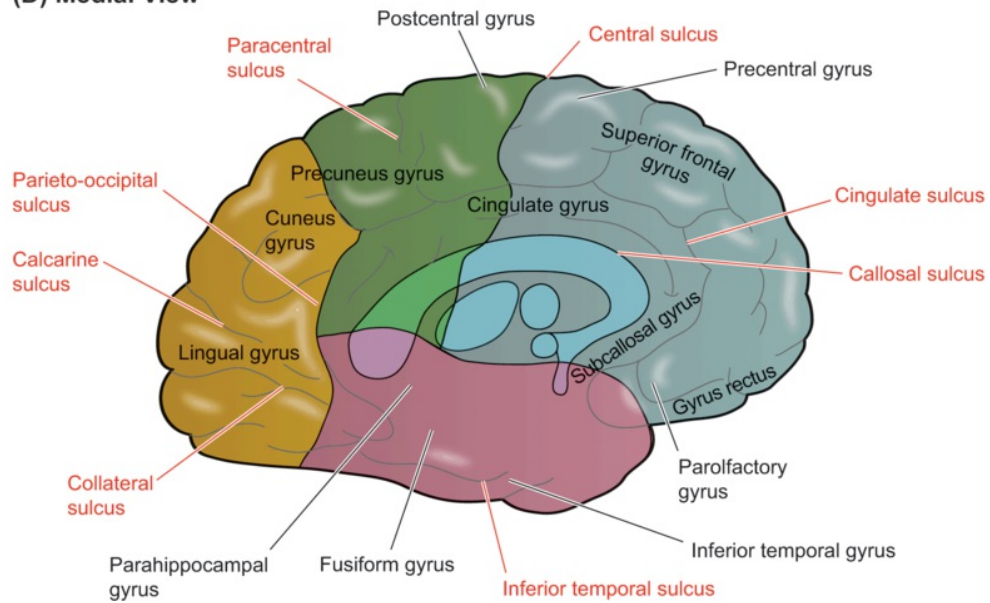
(B) Ventral View



(C) Lateral View



(D) Medial View



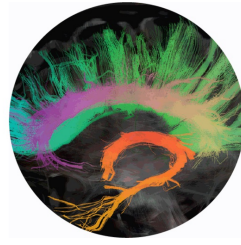
COGNITIVE NEUROSCIENCE

Updated fully, this accessible and comprehensive text highlights the most important theoretical, conceptual, and methodological issues in cognitive neuroscience. Written by two experienced teachers, the consistent narrative ensures that students link concepts across chapters, and the careful selection of topics enables them to grasp the big picture without getting distracted by details. Clinical applications such as developmental disorders, brain injuries, and dementias are highlighted. In addition, analogies and examples within the text, opening case studies, and “In Focus” boxes engage students and demonstrate the relevance of the material to real-world concerns. Students are encouraged to develop the critical thinking skills that will enable them to evaluate future developments in this fast-moving field. A new chapter on Cognitive Neuroscience and Society considers how cognitive neuroscience issues relate to the law, education, and ethics, highlighting the clinical and real-world relevance. An expanded online package includes a test bank.

Marie T. Banich uses brain imaging techniques to understand the neural systems that enable us to direct actions and thoughts in a goal-oriented manner, often referred to as executive function. Her research findings have been published in leading journals, including *Science*. Among her professional experiences, Professor Banich has been a member of the MacArthur Foundation on Adolescent Development and Juvenile Justice, a Fulbright Senior Scholar in Verona, Italy, and a recipient of a James Cattell sabbatical award. Currently she serves as the co-Principal Investigator for the Colorado site of the Adolescent Brain Cognitive Development study, an unprecedented 10-year longitudinal study that uses neuroimaging to provide an unrivaled window on development of the adolescent brain and its influences on cognitive and emotional development.

Rebecca J. Compton has taught at Haverford College since 1999 and in 2012 she received Haverford’s prestigious Lindback Award for Distinguished Teaching. She received her BA from Vassar College and her PhD in biological psychology from

University of Chicago. She is the recipient of several NSF and NIH grants for research in primarily undergraduate institutions and has served on the Education and Training Committee of the Society for Psychophysiological Research.



COGNITIVE NEUROSCIENCE

Marie T. Banich

University of Colorado Boulder

Rebecca J. Compton

Haverford College, Pennsylvania



CAMBRIDGE
UNIVERSITY PRESS



University Printing House, Cambridge CB2 8BS, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre, New Delhi – 110025, India

79 Anson Road, #06–04/06, Singapore 079906

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning, and research at the highest international levels of excellence.

www.cambridge.org

Information on this title: www.cambridge.org/9781107158443

DOI: [10.1017/9781316664018](https://doi.org/10.1017/9781316664018)

© Cambridge University Press 2018

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2018

Printed in the United States of America by Sheridan Books, Inc.

A catalogue record for this publication is available from the British Library.

ISBN 978-1-107-15844-3 Hardback

ISBN 978-1-316-50790-2 Paperback

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Contents

[Preface](#)

[Acknowledgments](#)

[Dedication](#)

[Part I Fundamentals](#)

[Chapter 1](#) [Introduction to the Nervous System](#)

[Chapter 2](#) [Historical Perspectives](#)

[Chapter 3](#) [Methods](#)

[Part II Neural Bases of Mental Functions](#)

[Chapter 4](#) [Motor Control](#)

[Chapter 5](#) [Sensation and Perception](#)

[Chapter 6](#) [Object Recognition](#)

[Chapter 7](#) [Spatial Cognition](#)

[Chapter 8](#) [Language](#)

[Chapter 9](#) [Memory and Learning](#)

[Chapter 10](#) [Attention](#)

Chapter 11 Executive Function and Higher-Order Thinking

Chapter 12 Emotion

Chapter 13 Social Cognition

Part III Broader Applications

Chapter 14 Psychopathology

Chapter 15 Brain Development and Plasticity

Chapter 16 Generalized Cognitive Disorders

Chapter 17 Cognitive Neuroscience and Society

Glossary

References

Index

Contents

[Preface](#)

[Acknowledgments](#)

[Dedication](#)

[Part I Fundamentals](#)

[Chapter 1 Introduction to the Nervous System](#)

[What Is Cognitive Neuroscience?](#)

[Basic Building Blocks of the Nervous System: Neurons and Glia](#)

[Neuroanatomical Terms and Brain “Geography”](#)

[Major Subdivisions of the Central Nervous System](#)

[Spinal Cord](#)

[Medulla: Control of Basic Functions](#)

[Cerebellum: Fluid Movement](#)

[Pons: A Connective Bridge](#)

[Midbrain: Orienting by Sound and Sight](#)

[Hypothalamus: Maintaining the Body’s Equilibrium](#)

[Thalamus: Gateway to the Cortex](#)

[Major Subcortical Systems: The Basal Ganglia and the Limbic System](#)

[Cerebral Cortex](#)

[A Closer Look at Neurons](#)

[Electrochemical Signaling in the Nervous System](#)

[Neurotransmitters](#)

[In Focus: Can Herbs Really Improve Your Memory, Attention, and Mood?](#)

Myelination

A Closer Look at the Cerebral Cortex

Cytoarchitectonic Divisions

Primary Sensory and Motor Cortices

Association Areas

White-Matter Tracts

Summary

Chapter 2 Historical Perspectives

Ancient Times Until the 1800s

The Twentieth Century: Heyday of the Lesion Method

Single-Case Versus Group Studies

Inferences That Can Be Drawn From the Lesion Method

Limitations of the Lesion Method

The 1960s, 70s, and 80s

Studies With Nonhuman Animals

In Focus: Discovery of the “Homunculus”

Electrophysiological Methods

Disconnection Syndromes

Split-Brain Studies

Hemispheric Specialization: Left Brain, Right Brain

In Focus: Left Out? Lateralization in Non-Right-Handers

The 1980s and 90s: The Advent of Brain Imaging

Anatomical Methods: Computerized Axial Tomography

Functional Methods: Positron Emission Tomography

The Twenty-First Century: The Brain Imaging Revolution

Summary

Chapter 3 Methods

Introduction

Participant Populations

Clinical Populations

Neurologically Intact Individuals

Techniques for Analyzing Behavior

The Role of Cognitive Theories

Assessment of Behavior in Brain-Damaged Populations

Techniques for Assessing Brain Anatomy: Structural Magnetic Resonance Imaging (sMRI)

The Basics of Magnetic Resonance Imaging (MRI)

Regional Brain Structure

Anatomical Connectivity

Techniques for Revealing Where in the Brain Activity Is Occurring

Neurochemical Methods: Positron Emission Tomography and Magnetic Resonance Spectroscopy

Oxygen-Related Methods: Functional Magnetic Resonance Imaging (fMRI)

In Focus: Participating in a Functional Magnetic Resonance Imaging Study

Electromagnetic Recording Methods

Electroencephalography

Event-Related Potentials

Magnetoencephalography

Optical Recording Methods

Techniques for Modulating Brain Activity

Transcranial Magnetic Stimulation (TMS)

Transcranial Direct Current Stimulation (tDCS)

Multilevel and Multi-Modal Approaches

Combining Computational and Neuroimaging Approaches

Summary

Part II Neural Bases of Mental Functions

Chapter 4 Motor Control

Introduction

Peripheral Control of Movement

Motor Tracts

Brain Structures Involved in Motor Control

Subcortical Regions

Cortical Regions

Integrated Models of the Motor System

In Focus: Using Brain Activation to Control Prosthetic Limbs

Motor Disorders

Subcortical Motor Disorders

Cortical Motor Disorders

Summary

Chapter 5 Sensation and Perception

The Retina

Photoreceptors

Ganglion Cells

Receptive Fields

Pathways From the Retina to the Brain

The Tectopulvinar Pathway

The Geniculostriate Pathway

Lateral Geniculate Nucleus

Layers of the LGN

Retinotopic Mapping in the LGN

Feedback Connections to the LGN

Primary Visual Cortex (Striate Cortex)

Organization of Striate Cortex

[Binocular Integration in Striate Cortex](#)

[Contextual Modulation of Cells in Striate Cortex](#)

[In Focus: Seeing What's Not There: Visual Illusions and the Striate Cortex](#)

[Visual Areas Beyond the Striate Cortex](#)

[Multiple Maps of the Visual World](#)

[Area V4: A Special Module for Coding Color?](#)

[Blindsight and the Visual Pathways](#)

[Divergence into the "What" and "Where" Pathways](#)

[Auditory Processing](#)

[Computational Problems in Audition](#)

[Organization of the Auditory Pathways](#)

[Brainstem Computation of Spatial Location](#)

[Organization of Auditory Cortex](#)

[Auditory-Visual Interactions](#)

[Conclusions](#)

[Summary](#)

Chapter 6 Object Recognition

[The "What" Ventral Visual System](#)

[Deficits in Visual Object Recognition](#)

[Apperceptive and Associative Agnosias](#)

[Prosopagnosia: Agnosia for Faces](#)

[Category-Specific Deficits in Object Recognition](#)

[Theoretical Issues in Visual Object Recognition](#)

[Sparse Versus Population Coding for Objects](#)

[The Problem of Invariance in Recognition](#)

[Feature-Based Versus Configural Coding of Objects](#)

[Category Specificity: Are Some Types of Stimuli More Special Than Others?](#)

Object Recognition in Tactile and Auditory Modalities

Agnosias in Other Modalities

Tactile Object Recognition

Auditory Object Recognition

What Versus Where Across Modalities

In Focus: Visual Imagery: Seeing Objects With the Mind's Eye

Summary

Chapter 7 Spatial Cognition

The Dorsal Visual System for Spatial Cognition

Anatomy of the Dorsal Stream

Cellular Properties in the Dorsal Stream

Coding for the Three Dimensions of Space

Distinguishing Left from Right

Depth Perception

Spatial Frames of Reference

Neural Coding of Reference Frames

Dissociability of Reference Frames

Categorical Versus Coordinate Spatial Relations

Motion Perception

Specific Neural Regions for Motion Perception

Incorporating Knowledge of Self-Motion

Space and Action

Constructional Abilities

Optic Ataxia

Neural Mechanisms for Sensory-Motor Integration

Spatial Navigation

In Focus: Are Numbers Spatial?

Navigational Skills

Neural Coding of Spatial Environments

Challenges to the Dorsal–Ventral Stream Dichotomy

Summary

Chapter 8 Language

Brain Systems for Auditory Language

Classic Neurological Conceptions

Psycholinguistic Perspectives

Evidence From Double Dissociations

Language Processing From a Network Perspective

Visual “Spoken” Language

Basic Structure of American Sign Language (ASL)

Neural Organization of ASL

In Focus: Brain Organization in Bilinguals

Neurological Bases for Visual Language Processing

Evidence From Studies of Patients With Brain Damage

Converging Evidence from Other Research Methods

Processing of Non-Indo-European Languages and Other Symbolic Systems

Kana and Kanji

Music

Right-Hemisphere Contributions to Language Processing

Prosody

Semantics

Narrative, Inference, and Metaphor

Summary

Chapter 9 Memory and Learning

What is Memory?

Hippocampal Damage Causes Amnesia, a Disorder of Long-Term Memory

Global Nature of the Deficit

[Temporal Profile of Affected Memories](#)

[Spared Abilities](#)

[Multiple Memory and Learning Systems](#)

[What Distinguishes Memory Systems?](#)

[Memory and Consciousness](#)

[Nonhippocampal Regions Involved in Memory and Learning](#)

[Domain-Specific Neocortical Regions: Initial Processing and Subsequent Access](#)

[The Basal Ganglia: Skill Learning](#)

[The Amygdala: An Interface Between Memory and Emotion](#)

[Anterior Temporal Regions: Amodal Storage of Semantic Information](#)

[Brain Systems For Different Stages of Memory](#)

[Encoding: The Medial Temporal Lobe and Prefrontal Regions](#)

[Consolidation and Storage: How Critical Is the Hippocampus?](#)

[Retrieval: Hippocampal, Prefrontal, and Parietal Mechanisms](#)

[In Focus: Does Sleep Help You to Remember?](#)

[Working Memory: The Ability to Hold and Manipulate Information On-Line](#)

[Patients With Deficits in Working Memory](#)

[Studies With Nonhuman Animals: A Role for Prefrontal Cortex?](#)

[Insights From Neurologically Intact Individuals](#)

[The Relationships Between Memory Systems](#)

[Theoretical and Computational Reasons for Distinct Memory Systems](#)

[Interacting Memory Systems for Different Types and Stages of Learning](#)

[Summary](#)

Chapter 10 Attention

[What Is “Attention”?](#)

[Brain Structures Mediating Arousal](#)

[Brain Structures Mediating Vigilance and Sustained Attention](#)

[Selective Attention](#)

[The Time Course of Attentional Selection](#)

[Brain Regions Mediating Selective Attention](#)

[Sources and Sites of Attentional Control](#)

[Neural Mechanisms of Selection: Biased Competition](#)

[Neural Bases of Divided Attention](#)

[In Focus: Pay Attention to the Road!](#)

[Network Models of Attentional Control](#)

[A Distributed but Overlapping Network](#)

[Altering, Orienting, and Executive Attention](#)

[Selection of Goals Versus Detection of Behaviorally Relevant Stimuli](#)

[The Default Network: The Lack of Attention or Internal Attention?](#)

[Hemineglect: Clinical Aspects](#)

[Clinical Features](#)

[Theories Regarding the Underlying Deficit](#)

[Treatment](#)

[Hemineglect: Implications for Understanding Brain–Behavior Relationships](#)

[Attention Based on Objects](#)

[Hemispheric Differences in Attentional Control](#)

[Processing of Unattended Stimuli](#)

[Consciousness](#)

[Summary](#)

Chapter 11 [Executive Function and Higher-Order Thinking](#)

[Theoretical Perspectives](#)

[Controlled Versus Automatic Processes](#)

Goal-Centered Processing

Multifactor Models

Goal-Directed Behaviors

Initiation of Behavior

Creation and Maintenance of a Goal or Task Set

Sequencing and Planning

Shifting Set and Modifying Strategies

Self-Monitoring and Evaluation

Inhibition

In Focus: Can You Inhibit a Memory?

Higher-Order Thinking

Abstract and Conceptual Thinking

Rules and Inference

Response to Novelty

Judgment and Decision Making

Organization of the Brain for Executive Function

A Central Role for Working Memory in Executive Function

Summary

Chapter 12 Emotion

Subcortical Contributions to Emotion

Fight-or-Flight Response

Fear and Emotional Learning

Reward and Motivation

In Focus: The Pleasure of Music

Cortical Contributions to Emotion

Representing Bodily Cues of Emotion

Integrating Emotion and Action

Incorporating Emotion into Decision Making

Regulating Emotion

[Communicating and Interpreting Emotional Signals](#)

[Models of Emotional Experience](#)

[Summary](#)

Chapter 13 [Social Cognition](#)

[Social Influence](#)

[Conformity](#)

[Social Norm Compliance](#)

[Understanding Other Minds](#)

[Imitation and Simulation](#)

[Theory of Mind](#)

[Empathy](#)

[Self Versus Other](#)

[Autism and Social Cognition](#)

[In Focus: The Pain of Rejection](#)

[Perceiving and Judging Social Groups](#)

[In-group-Out-group Effects](#)

[Stereotyping and Prejudice](#)

[Stereotype Threat](#)

[Summary](#)

Part III [Broader Applications](#)

Chapter 14 [Psychopathology](#)

[Schizophrenia](#)

[Symptoms and Features](#)

[Frontal Lobe](#)

[Temporal Lobe](#)

[Disruption in Functional Connectivity](#)

[What Causes Schizophrenia?](#)

[Implications for Treatment](#)

[Depression](#)

[Symptoms and Features](#)

[Frontal Lobe](#)

[Posterior Cortical Regions](#)

[Functional Connectivity Among Cortical Regions](#)

[Subcortical Regions](#)

[Therapeutic Interventions](#)

[In Focus: Can Your Genes Make You Unhappy?](#)

[Anxiety Disorders](#)

[Symptoms and Features](#)

[Amygdala and Hippocampus](#)

[Cortical Regions](#)

[Action Systems in Obsessive-Compulsive Disorder](#)

[Substance Abuse and Addiction](#)

[Reward Pathways](#)

[Orbitofrontal Cortex](#)

[Other Brain Regions Implicated in Addiction](#)

[Conclusions and Caveats](#)

[Summary](#)

Chapter 15 [Brain Development and Plasticity](#)

[Development of the Brain](#)

[Changes in the Brain During Childhood](#)

[Changes in the Brain During Adolescence](#)

[Influence of the Environment on the Developing Brain](#)

[Developmental Disorders](#)

[Intellectual Disability](#)

[Dyslexia](#)

[Autism](#)

[Attention-Deficit/Hyperactivity Disorder](#)

[Brain Plasticity in Adulthood](#)

[Recovery of Function Following Brain Damage](#)

[Neurophysiological Responses to Insult](#)

[Regional Mechanisms for Recovery of Function](#)

[Recovery of Function in Adults](#)

[Recovery of Function in Children](#)

[In Focus: Can Deprivation in One Sensory Modality Promote Extraordinary Abilities in Another?](#)

[Changes in the Brain With Aging](#)

[Cognitive Changes With Aging](#)

[Neural Changes With Aging](#)

[Slowing the Effects of Aging](#)

[Summary](#)

Chapter 16 [Generalized Cognitive Disorders](#)

[Closed Head Injury](#)

[Etiology](#)

[Neuropsychological Consequences](#)

[Intervention](#)

[In Focus: Closed Head Injury and Sports](#)

[Dementing Diseases](#)

[Cortical Dementias](#)

[Subcortical Dementias](#)

[Mixed-Variety Dementias](#)

[Multiple Sclerosis](#)

[Epilepsy](#)

[Disorders of Conscious Awareness](#)

[Summary](#)

Chapter 17 Cognitive Neuroscience and Society

Public Perceptions of Neuroscience

Neuroscience and Education

Neuroscience and Social Inequality

Neuroscience and the Law

In Focus: Can Brain Imaging Detect Lies?

Neuroscience and Performance Optimization

Neuroscience and the Marketplace

The Neuroscience of Morality

Summary

Glossary

References

Index

Preface

THE FOURTH EDITION of this book, although extensively revised, retains the spirit, organization, and many of the features of the first three editions. Like the earlier editions, it provides a systematic introduction to the neural basis of mental function. It includes state-of-the-art research from experimental work performed with humans and animals, as well as findings from clinical populations. The goal, as before, is to provide a balanced, synthesized, and integrated view of what we know both about the brain and about cognition. Simultaneously, the text aims to provide these views in accessible prose that will excite students to think critically about the potential of cognitive neuroscience to yield new insights.

While the entire text has been revised and updated, two sets of major changes are especially notable. First, the content of the book has been modified in line with the changing nature of the field. The introductory chapters have been reorganized to provide an integrated overview of the nervous system at both cellular and neuroanatomical levels in [Chapter 1](#), followed by a new chapter on the historical development of cognitive neuroscience ([Chapter 2](#)). Two new chapters have been included, one on Social Cognition ([Chapter 13](#)) and another on Cognitive Neuroscience and Society ([Chapter 17](#)). The inclusion of these chapters reflects rapid expansions in new research in these subfields combined with awareness of the need for cognitive neuroscientists to address questions of societal interest. In addition, material on hemispheric specialization from prior editions has been integrated with coverage throughout the text, rather than parceled into a separate chapter as in prior editions. Second, the book has been revised to make the content more accessible to students. It has been rewritten to

focus on major concepts and to present them, and the experiments that support them, in a way that makes the critical ideas clear to students without bogging them down in detail. Finally, recognizing the importance of visual elements in learning, the four-color art program has been completely revised with an expanded set of figures in every chapter.

In addition to these major changes, every chapter has been thoroughly updated to reflect current findings in the fast-growing field of cognitive neuroscience. While the current edition still includes findings from traditional methods, such as the study of brain-damaged patients, which have provided foundational knowledge to the field, we pay special attention to the integration of findings from a variety of newer approaches, including transcranial magnetic stimulation, diffusion tensor imaging, multi-voxel pattern analysis, and studies examining functional connectivity. Throughout, our intention is to provide students with a thorough and solid grounding in the basic principles and findings of cognitive neuroscience, tools that they can then use to further understand applied and clinical problems.

Text Organization and Features

The book's soul remains very much the same as in the first three editions, as the following main features have been retained.

■ The book provides a systematic survey of the neural bases of a wide variety of mental functions

The overall organization of the book is divided into three main sections: fundamentals ([Chapters 1–3](#)), neural bases of specific mental functions ([Chapters 4–13](#)), and broader applications ([Chapters 14–17](#)). The first part of the book, comprising the first three chapters, provides students with a basic foundation for the exploration of cognitive neuroscience. The [first chapter](#) provides information about the basic parts and divisions of the central nervous system and the fundamentals of neural transmission. This chapter may be unnecessary for students who have already completed a course in physiological psychology, but will be of use to students who have not. The [second chapter](#) outlines the historical milestones in the development of the field, with special attention to methodological and conceptual developments that advanced the field in different eras. The [third chapter](#) acquaints students with the myriad of burgeoning techniques, both standard and novel, that are available to scientists and clinicians in their quest to understand the neural bases of mental function.

The second part of the book, [Chapters 4](#) through [13](#), provides a survey of the neural bases of mental function, with each chapter devoted to a distinct mental function. The chapter topics discussed are, in order, motor processes, early perceptual processing, object recognition, spatial cognition, language, memory, attention, executive function, emotion, and social cognition.

The last part of the book, comprising the last four chapters, examines broad-based applications in cognitive neuroscience, including development, aging, clinical syndromes, and the interface between neuroscience and society. Instructors may view these chapters as more discretionary than earlier ones, in the sense that they cover more advanced issues. In our teaching, we've found that these advanced, applied, and clinical issues are of special interest to many students, as they find it very rewarding to use the knowledge that they have gained earlier in the text to approach these broader applications. [Chapter 14](#) examines mental conditions such as schizophrenia, depression, anxiety disorders, and substance abuse from a cognitive neuroscience perspective.

[Chapter 15](#) examines neural plasticity from a lifespan perspective, including developmental changes during childhood, adolescence, and aging. In addition, it discusses recovery of function in children and in adults, and the neural bases of developmental disabilities. [Chapter 16](#) examines syndromes that are characterized by generalized cognitive disorders (rather than the more localized and specific disorders discussed in [Chapters 4](#) through [13](#)), including closed head injury, dementia, demyelinating diseases, and epilepsy. Finally, the text ends with [Chapter 17](#), Cognitive Neuroscience and Society, which critically examines the ways in which cognitive neuroscience knowledge can be applied to domains of broad societal concern such as education, social inequality, the law, and morality.

■ The sequence of the chapters is designed for progressive learning

The chapters have been carefully sequenced so that information in later chapters builds upon information in earlier ones. Notably, the processes most linked to motoric and sensory functions are presented earlier, and those that depend on more integrative aspects of brain function, such as executive function and emotion, are presented later. For example, the chapter on object recognition directly precedes that on spatial processing, so that the student is introduced to the ventral and dorsal visual processing streams in consecutive chapters. The chapter on memory is preceded by the language and object-recognition chapters so that the distinction between generalized memory disorders and the “memory” problems that are specific to certain domains (e.g., anomia in language or agnosia with regard to objects) is clear. Yet, despite the intentional progression of ideas across chapters, chapters are written to be self-contained so that instructors may alter the order of material depending on specific syllabus needs.

■ The book is designed to actively engage students in the process of learning

Most chapters begin with an opening case history to pique the students' interest and preview issues that are discussed later in the chapter. For example, the opening case history in [Chapter 4](#) discusses how Muhammad Ali's boxing career led him to have a Parkinsonian disorder, and the opening case history in [Chapter 16](#) discusses the mental decline of Marie's maternal grandmother due to dementia. The text is written in a conversational tone rather than in a technical style, to grab the students' interest and retain it. We use analogies extensively so that difficult conceptual issues can be presented in a tractable manner. Each chapter includes an "In Focus" box that explores in depth a specific applied issue in cognitive neuroscience, helping students to see the implications of research for everyday life.

To keep students oriented to terminology, key terms are introduced in boldface and defined in a glossary at the back of the book. Chapter summaries allow students to review the material learned or preview what is to be discussed, and outlines at the beginning of each chapter provide a clear conceptual structure of the contents. All these features are designed to make this book as user-friendly as possible.

■ State-of-the-art knowledge in the field is presented without sacrificing accuracy or oversimplifying the material

As researchers who maintain highly active and visible research programs, we are in a position to ensure that the book contains not only a discussion of the "classic" findings in the field, but also the cutting-edge portion of our knowledge. Never, however, are students overwhelmed with a laundry list of findings or with overly technical arcane issues. Rather, representative studies are used to highlight the nature of current debates, so that students can understand, and think critically about, the conceptual issues under consideration and how researchers attempt to reason based on experimental evidence. Our extensive work in both research and teaching in cognitive neuroscience allows us to

present issues in a manner that is precise and sophisticated, yet also accessible and integrative.

What's New in This Edition

While the approach of the prior editions has been retained, this fourth edition has nevertheless been extensively revamped. The main new additions are as follows.

■ The use of an integrated four-color art program

With this edition, we have thoroughly revised the art program, emphasizing systematic depiction of information across the figures, so as to enhance students' ability to understand the material. All figures from earlier editions have been redrawn, and many new figures have been added. Some figures highlight regions of the brain so the reader can quickly see "where" and "what" in the brain are important. Other figures present data from representative studies in the field, so that students can gain experience in viewing and interpreting data; still others depict important experimental paradigms so that students can quickly grasp how a key study was conducted.

■ Addition of two new chapters

Two chapters have been added to the text to reflect growing areas of research over the last decade. A new stand-alone chapter covering social cognitive neuroscience ([Chapter 13](#)) is now included due to the burgeoning growth of research in this area. In the previous edition of the text, this material was relegated to a relatively short section of the chapter on Emotion. The new Social Cognition chapter addresses how new knowledge from neuroscience expands our understanding of how we perceive the mental states of other people, categorize people into social groups, and control our behavior to align with social norms.

In addition, completely new to this edition is [Chapter 17](#), Cognitive Neuroscience and Society. This chapter, which concludes the book, covers issues of broader societal

significance to which the field can speak. For example, the chapter addresses research on how laypeople view neuroscience research, what neuroscience may add to our understanding of the effects of social inequality on development, and how neuroscience knowledge is being used in criminal justice settings. As students of cognitive neuroscience enter a wide range of professions, such as law, education, and business, it is crucial for them to be able to critically evaluate what neuroscience can and cannot add to discussions of issues in these arenas.

■ Extensive updating of the material to incorporate the acceleration of knowledge in the field

The field of cognitive neuroscience continues to explode with new discoveries. As a result, all of the chapters of the book were extensively rewritten to incorporate this vast amount of additional knowledge, which is reflected in hundreds of new references from studies using diverse methodologies.

Acknowledgments

This book has benefited greatly from the generous help of many colleagues who reviewed it. We were genuinely touched by the time and effort that these people, listed below, took to share their expert advice to improve the book for the fourth edition. Their enthusiasm for the project bolstered us and kept us on our toes. Although we may not have taken all of their advice, we thought carefully about every one of their suggestions. We are most appreciative of their input. We also thank Doug Bernstein and Phil Meneely for their insights and wisdom regarding the textbook publishing process, which spared us many headaches. In addition, we thank the reviewers of prior editions; although they are too numerous to be listed here, their contributions helped to build a solid foundation upon which this new edition could be built. We thank the following reviewers for their comments on both the content and presentation of the material in the book, which we found invaluable: David Badre, Brown University; Erin Bigler, Brigham Young University; Kyle Cave, University of Massachusetts; Rosie Cowell, University of Massachusetts; Laurie Cutting, Vanderbilt University; Erica Dixon, American University; Russ Epstein, University of Pennsylvania; Kelly Goedert, Seton Hall University; Elizabeth Heaton and Averil Gaines, Haverford College; Greg Hickok, University of California, Irvine; Tiffany Ito, University of Colorado; Sabine Kastner, Princeton University; Mary Ellen Kelly, Haverford College; Ben Levy, University of San Francisco; Jared Medina, University of Delaware; Eric Pakulak, University of Oregon; Ken Paller, Northwestern University; Cathy Reed, Claremont-McKenna College; Gretchen Reeves, Eastern Michigan University; Paige Scalf, Durham

University; Rachael Seidler, University of Michigan; Penny Seymoure, Carthage College; Rebecca Sifton, Loyola University.

Finally, we are most grateful to the superb editorial staff at Cambridge. Matthew Bennett inspired us and guided us through our conceptual approach to the revisions; Claire Eudall skillfully shepherded us through chapter revisions with impressive attention to detail as well as patience and good humor; Charles Howell supervised the production of the manuscript with impressive professionalism; and Simon Tegg brought our ideas for illustrations to life. It was wonderful to have our materials in the hands of such outstanding editors. As this is the fourth edition of the book, it builds on editorial advice we have received on previous editions from Jane Knetzger, Danielle Richardson, and Tali Beesley, respectively, and the support of Jane Potter, whom we thank as well.

In the end, we were able to write this book not only due to the professional contributions of all the people named above, but also due to those who personally inspired and supported us. Those include our families – Jeremy Meyer, Gwen Compton-Engle, David Compton, Laura Edwards – and, most importantly, our mothers, Serafina Banich and Judy Ellis, to whom we dedicate this book. We conclude here with words of dedication from each of us to the women who taught us to be who we are.

From Marie

I have been incredibly fortunate to be my mother's daughter. She was my first and best teacher, and through the decades someone whose perspective has enlivened my life immeasurably. If we are lucky in life, one's path crosses with a mythic figure who teaches us and shapes us, but who more importantly shows us the magical possibilities that exist right under our noses in our seemingly very unmagical and everyday world. My mother has been that mythic figure to me. Countless times she has unmasked for me those treasures that I would have inadvertently trod over, such as pointing out the brush

strokes in a painting used to convey the delicacy of a flower's petals, or selecting the perfect word to convey the richness and complexity of an idea.

While my mother's love of learning and expertise in education spurred, in part, my desire to write a textbook, it has been these last five years since her stroke during which she has taught me the most. Through her stroke, I was confronted in a very visceral and personal way with both the expanse and limits of my knowledge about the brain. Working with her to recover what abilities she could, and grieving with her in the abilities forever lost, has been a partnership unlike any other I have ever experienced.

I will always be grateful to her for her patience as I pushed and probed to understand the new and restricted landscape of her mind, even though at times it laid her deficiencies bare. And I appreciated her understanding and fortitude, especially during those times when I purposely steered her into mental waters that I knew, while once familiar, were now foreign. She was willing to be taken there to struggle through her sea of confusion, as she knew its purpose was to try and encourage her brain to reconnect to knowledge it once had. But mostly I am honored that she trusted me to try my best not to let her drift too long nor without aim or reason.

If I am lucky, my mother will be around for the next edition of this textbook. Because even as she marches into the middle of her tenth decade on this earth, she continues to teach me something with each of our interactions.

From Rebecca

My mother taught me how to use my brain. She taught me to look at the world with wonder and joy. A former high school chemistry teacher, social worker, university administrative assistant, jack-of-all-trades – one who might have been an engineer in a different era of opportunity for women – she always conveyed a fascination with “how things work” that I later rediscovered in my own love affair with the brain. Through her example, she taught me that women can enjoy tinkering with mechanical things, that they can ride their bikes without worrying about mussing their hair, that they can have an

excellent sense of direction, that they can make of themselves what they want to be. Most importantly, though, she continues to teach me that in the end, achievement isn't measured in the number of pages published, grants obtained, or status acquired, but rather in a person's compassionate actions in the world. I strive to live up to her example.

Marie T. Banich

Rebecca J. Compton

To my (left-handed) mom,

Who after her stroke displayed so much grace and grit,

And who in her brain-damaged state has taught me so much more than I ever could have imagined not only about the intricacies and resilience of the human brain, but also about the human spirit.

M.T.B.

To mom, who continues to teach me all of the important things in life.

R.J.C.

Part I



Fundamentals

Chapter 1 [Introduction to the Nervous System](#)

Chapter 2 [Historical Perspectives](#)

Chapter 3 [Methods](#)

Chapter 1

Introduction to the Nervous System



[What Is Cognitive Neuroscience?](#)

[Basic Building Blocks of the Nervous System: Neurons and Glia](#)

[Neuroanatomical Terms and Brain “Geography”](#)

[Major Subdivisions of the Central Nervous System](#)

[Spinal Cord](#)

[Medulla: Control of Basic Functions](#)

[Cerebellum: Fluid Movement](#)

[Pons: A Connective Bridge](#)

[Midbrain: Orienting by Sound and Sight](#)

[Hypothalamus: Maintaining the Body’s Equilibrium](#)

[Thalamus: Gateway to the Cortex](#)

[Major Subcortical Systems: The Basal Ganglia and the Limbic System](#)

[Cerebral Cortex](#)

[A Closer Look at Neurons](#)

[Electrochemical Signaling in the Nervous System](#)

[How Information Is Transferred Within a Neuron](#)

[How Information is Transferred Between Neurons](#)

[How Postsynaptic Potentials Can Cause an Action Potential](#)

[Factors That Modulate a Neuron’s Response](#)

[Neurotransmitters](#)

[Amino Acids: Glutamate and Gamma-Aminobutyric Acid \(GABA\)](#)

[Neurotransmitter Systems](#)

[Interaction Between Neurotransmitter Systems](#)

[In Focus: Can Herbs Really Improve Your Memory, Attention, and Mood?](#)

[Myelination](#)

[A Closer Look at the Cerebral Cortex](#)

[Cytoarchitectonic Divisions](#)

[Primary Sensory and Motor Cortices](#)

[Motor Cortex](#)

[Somatosensory Cortex](#)

[Visual Cortex](#)

[Auditory Cortex](#)

[Olfactory and Gustatory Cortex](#)

[Association Areas](#)

[Frontal Lobe](#)

[Parietal Lobe](#)

[Temporal Lobe](#)

[White-Matter Tracts](#)

[Summary](#)

What Is Cognitive Neuroscience?

In this book, we explore how the neurological organization of the brain influences the way people think, feel, and act. [Cognitive neuroscience](#) is critical to our understanding of this linkage between brain and mind. Cognitive neuroscience comprises investigations of all mental functions that are linked to neural processes, ranging from investigations in animals to humans and from experiments performed in the laboratory to computer simulations. Much of the early work in this area comes from [human neuropsychology](#), which also focuses on understanding mental processes in humans, but with an emphasis on examining the changes in behavior as a result of brain trauma.

Since the mid-1970s, our knowledge in the realm of cognitive neuroscience and neuropsychology has grown rapidly, and so has the number of scientists and clinicians who specialize in these areas of inquiry. Cognitive neuroscientists attempt to understand the relationship between the brain and mind from a variety of conceptual vantage points simultaneously. Borrowing from computer science, they view the brain as an information processing system whose primary goal is to solve problems. These scientists attempt to understand how the brain is organized to perform specific computations, such as recognizing a face. To do so, they rely on integrating findings from different approaches. For example, they record the activity of cells to determine what stimulus makes the cells respond, use brain imaging to ascertain exactly which brain regions become active during a specific mental task, and build computer models to provide principles and gain insights into how different mental operations might be performed by the brain.

Experimental neuropsychologists work to understand the neural bases of cognition by doing scientific studies comparing individuals who have sustained brain damage with those who are neurologically intact. These researchers use a variety of techniques to divide complicated mental functions into meaningful categories, such as language and memory, and to isolate the contribution of specific brain regions to each of these functions.

Clinical neuropsychologists work in health care settings, such as hospitals and clinics, with individuals who have sustained brain damage through either trauma or disease. They diagnose the cognitive deficits resulting from brain trauma, plan programs of rehabilitation, evaluate the degree to which a patient is regaining function, and determine how environmental factors (e.g., family structure, educational background, and so forth) may moderate or exacerbate the effects of brain dysfunction. In this book, we provide an overview of the current state of knowledge in cognitive neuroscience as derived from findings in both the laboratory and the clinic.

The endeavor of understanding the relationship between the brain and the mind may be undertaken from two distinct vantage points, one that emphasizes the neurological

organization of the brain and one that emphasizes the psychology of the mind. The neurologically oriented approach emphasizes the brain's anatomy; therefore, the major objective of this approach is to understand the function of specific circumscribed regions of brain tissue. For instance, a researcher might want to investigate a particular brain structure, such as the hippocampus, to determine its anatomical characteristics, its connections to other brain regions and the pattern of that connectivity, and its role in mental functioning. Information derived from this approach can be extremely useful to medical personnel such as neurosurgeons who need to know what functions might be affected by different surgical approaches.

In contrast, the psychologically oriented approach emphasizes the brain's mental capabilities. The major objective of this approach is to understand how different aspects of cognition, such as language, memory, and attention, are supported by the neurological organization of the brain. For example, cognitive neuroscientists may want to know whether the brain structures supporting the ability to read are the same as, or distinct from, those supporting the ability to write. One way of addressing this question is to determine whether the pattern of brain activation observed when people are reading is distinct from that observed when they are writing.

In this book we lean more toward the psychologically oriented approach than the neurologically oriented one. This bias can be seen most clearly by taking a quick glance at the table of contents, which includes chapter titles such as "Language," "Memory," and "Attention," indicating that our discussion of the relationship between the brain and the mind emphasizes cognitive functions. If this book were written from a more neurologically oriented approach, the chapters would have been organized by brain regions and been titled "The Basal Ganglia," "The Cerebellum," and "The Frontal Lobes." Although we take a more psychologically oriented approach, a working knowledge and understanding of the neurological organization of the brain is indispensable, for only with that knowledge can we intelligently discuss the relationship

between psychological functions and the specific regions of brain tissue that support those functions.

Now is a particularly exciting time to study cognitive neuroscience. Vast advances in our knowledge in neuroscience, medical science, cognitive psychology, and computer science provide the opportunity to synthesize findings in ways that were impossible just a few years ago. Research in cognitive psychology has tremendously increased the sophistication of models of mental functioning. For example, we can take a complicated function such as language and divide it into specific subcomponents and subprocesses. At the same time, incredible advances in medical technology now allow us to examine the neuroanatomy and physiological functioning of the brain in ways unimagined even as recently as two decades ago. We discuss these advances in methods in more detail in [Chapter 3](#).

Before we begin to attempt to link cognitive functions to the brain, however, we need a common base of knowledge about the anatomy and physiology of the brain. This chapter is designed to provide this knowledge base. The first part of the chapter introduces the vocabulary scientists use when discussing the brain – the terms that describe the location of brain structures and their characteristics – as well as the major building blocks and subdivisions of the nervous system. The second part takes a closer look at the brain at both a micro and a macro level. We discuss how nerve cells communicate with one another and how disruptions in this process can have important implications for mental functions. The [final section](#) provides more details about the major lobes of the cerebral cortex and their associated mental functions.

Basic Building Blocks of the Nervous System: Neurons and Glia

The human nervous system, which consists of the brain, spinal cord, nerves, and ganglia, controls the body's response to internal and external stimuli. It is comprised of two main classes of cells: neurons and glia. [Neurons](#) are the cells in the nervous system

that carry information from one place to another by means of a combination of electrical and chemical signals. **Glia**, which outnumber neurons by at least 10 to 1, are support cells.

Neurons have three main parts: a dendritic tree, a cell body, and an axon (see [Figure 1.1](#)). The **dendritic tree** is the part of the neuron that receives input from other cells. The **cell body** is the part of the cell containing the nucleus and other cellular apparatus responsible for manufacturing the proteins and **enzymes** that sustain cell functioning. The **axon** is the appendage of the cell along which information is carried. It can vary in length; in some cases it is very short, extending not much further than the length of the dendrites and cell body. In other instances the axon is very long, spanning large distances between brain regions.

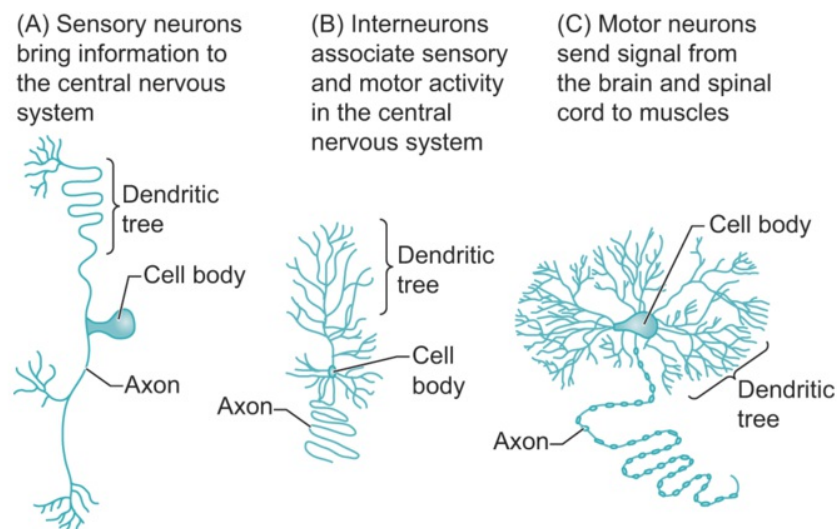


Figure 1.1 Examples of some nervous system cells (not to scale).

(A) Sensory neurons, (B) interneurons, and (C) motor neurons. Note that the appearance of the different kinds of neurons is distinctive; the appearance of each kind of neuron is due to its function. A sensory neuron collects information from a source and passes it on to an interneuron. The many branches of interneurons suggest that they collect information from many sources. Motor neurons are distinctively large and collect information from many sources; they pass this information on to command muscles to move.

Some neurons, known as sensory neurons, bring information to the central nervous system. Others, known as interneurons, associate information within the central nervous system. Finally, there are motor neurons, which send information from the brain and spinal cord to the muscles. Although all neurons have these same basic component parts, they come in a variety of sizes and shapes ([Figure 1.1](#)). We examine neurons in more detail later in the chapter, when we present a bit more information about how they work. When doing so, we highlight those aspects of neuronal function that are important for discussions in later chapters.

Compared to that of neurons, our knowledge about glia is relatively scant. Nonetheless, new knowledge has revealed that glia are much more than just “bit-part” players overshadowed by the leading role that neurons play in the nervous system. Although glia are not the main carriers of information, they are critical to the functioning of the nervous system. They influence the communication between neurons by modifying the chemical milieu between them, as well as refining and sculpting the physical connections between neighboring neurons. Developmentally, glia guide neurons as they migrate from the site of creation to their final position within the brain. Glia also aid with reorganization after brain damage by removing dead neurons, and they serve some of the nutritive needs of neurons and provide structural support (Zuchero and Bares, [2015](#)).

Glia are also critical to maintaining the [blood-brain barrier](#), which is the mechanism by which many harmful substances, such as toxins, are prevented from reaching the brain. The blood-brain barrier consists of tightly packed glial cells between blood vessels and neurons. This creates a physical obstruction that keeps not only toxins, but also nutrients, drugs, and immune system cells in the bloodstream from directly reaching the nervous system ([Figure 1.2](#)). As you can see, although glia are not directly responsible for transmitting information across the nervous system, such transmission would be impossible without them.

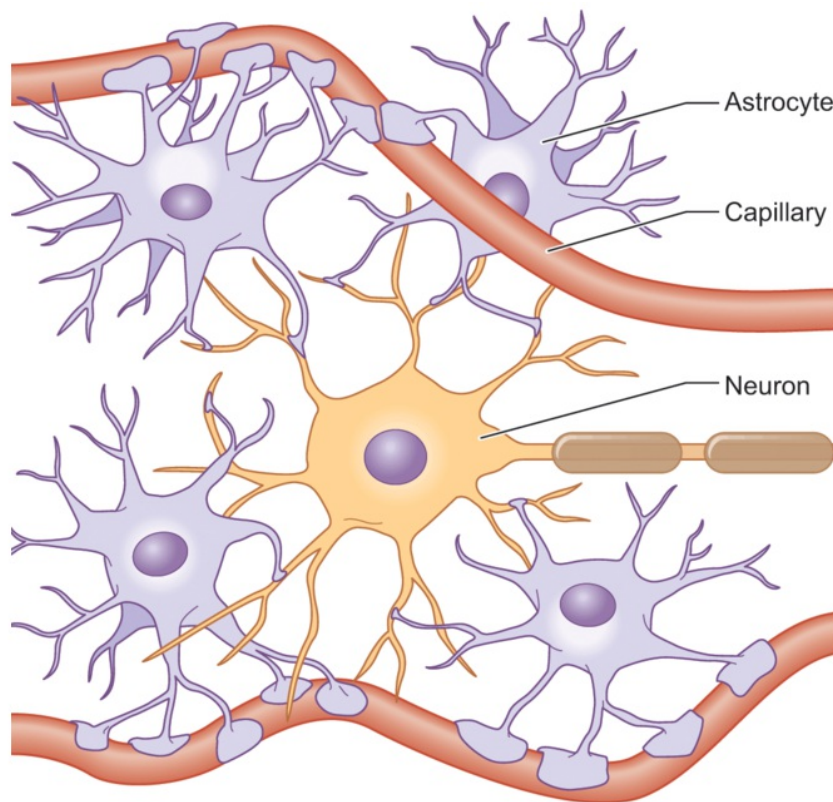


Figure 1.2 The relationship between glia and neurons.

Glia support the cell in many different ways. As shown here, they provide a support matrix around the neuron. In addition, by their close association with the blood supply they help to maintain the blood–brain barrier.

Neuroanatomical Terms and Brain “Geography”

Anytime you begin a long journey, you need a road map to guide your path, plus some understanding of common directional terms such as north, south, east, and west. So, to begin our trip around the “geography” of the central nervous system, we must identify the major neural regions and introduce terms that can help to orient us during the journey. Distinguishing between regions of the central nervous system, and in particular the brain, serves a function similar to drawing boundary lines on a map. Such lines on a map may tell us about differences in the geography of different regions, and also about differences in the behavior, attitudes, and customs of the people on either side of a boundary. Likewise, boundaries between brain regions are often drawn to demarcate

differences in the structure and function of brain tissue. Sometimes boundaries between brain regions are based on large and obvious anatomical landmarks, similar to major geographical features such as rivers or mountains on a map. In other cases, the physical distinction between regions is not obvious from the neuroanatomical terrain.

We must first learn the anatomical equivalents of north, south, east, and west. Unlike most geographical maps, which have only two dimensions, the brain has three. Thus, we need terms not only for the brain's left, right, top, and bottom, but also for its back and front. The front of the brain is referred to as [anterior](#) and the back as [posterior](#). Because the head of an animal is situated in front of its tail, regions toward the front can be referred to as [rostral](#) (toward the head), whereas regions toward the rear are referred to as [caudal](#) (toward the tail). The top of the brain is referred to as [superior](#), and the bottom is referred to as [inferior](#). In the human brain, [dorsal](#) and [ventral](#) have meanings similar to superior and inferior, respectively. However, in other portions of the central nervous system, such as the spinal cord, dorsal and ventral are better understood in reference to a four-legged animal or a fish. In these cases, dorsal means toward an animal's back, whereas ventral means toward an animal's stomach. If you have aquatic interests, you can remember that dorsal means top because the dorsal fin of a shark sticks out of the water. Finally, areas in the middle or center of the brain are referred to as [medial](#), whereas areas that are toward the outside of the brain are called [lateral](#) ([Figure 1.3](#)).

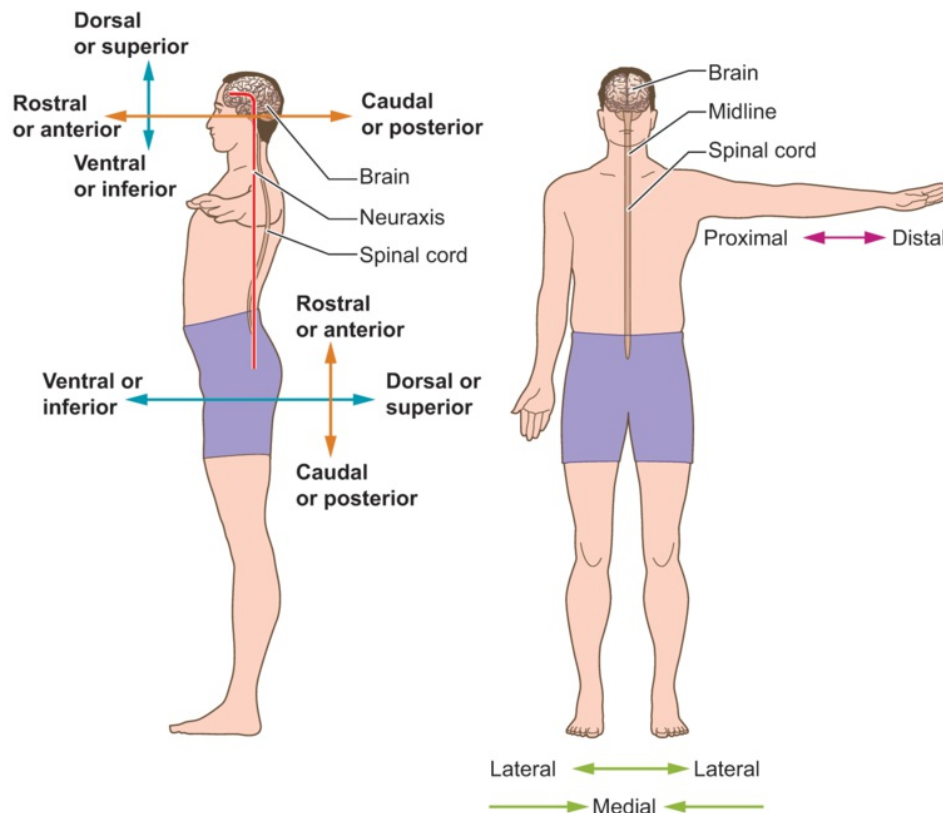


Figure 1.3 Anatomical terms for directions.

(Left) In a four-legged animal, dorsal/superior and ventral/inferior typically refer to the areas toward the back and stomach respectively, as shown at the hips of the figure on the left. However, because humans walk upright instead of on all fours, dorsal/superior and ventral/inferior also refer to the top and bottom of the head, respectively. (Right) Shown here are anatomical directions relative to the body midline.

Throughout this text, the brain is portrayed in one of three planes. When the brain is sliced ear-to-ear to separate the front from the back, the view is [coronal](#). If the brain is sliced so that the top of the brain is separated from the bottom, the view is [horizontal](#) (also sometimes referred to as axial or transverse). Finally, if the brain is cut so that the left side of the brain is separated from the right side, the view is [sagittal](#). A sagittal slice down the middle of the brain is known as a [midsagittal](#), or medial, section, whereas a section taken more toward one side is known as a lateral section ([Figure 1.4](#)).

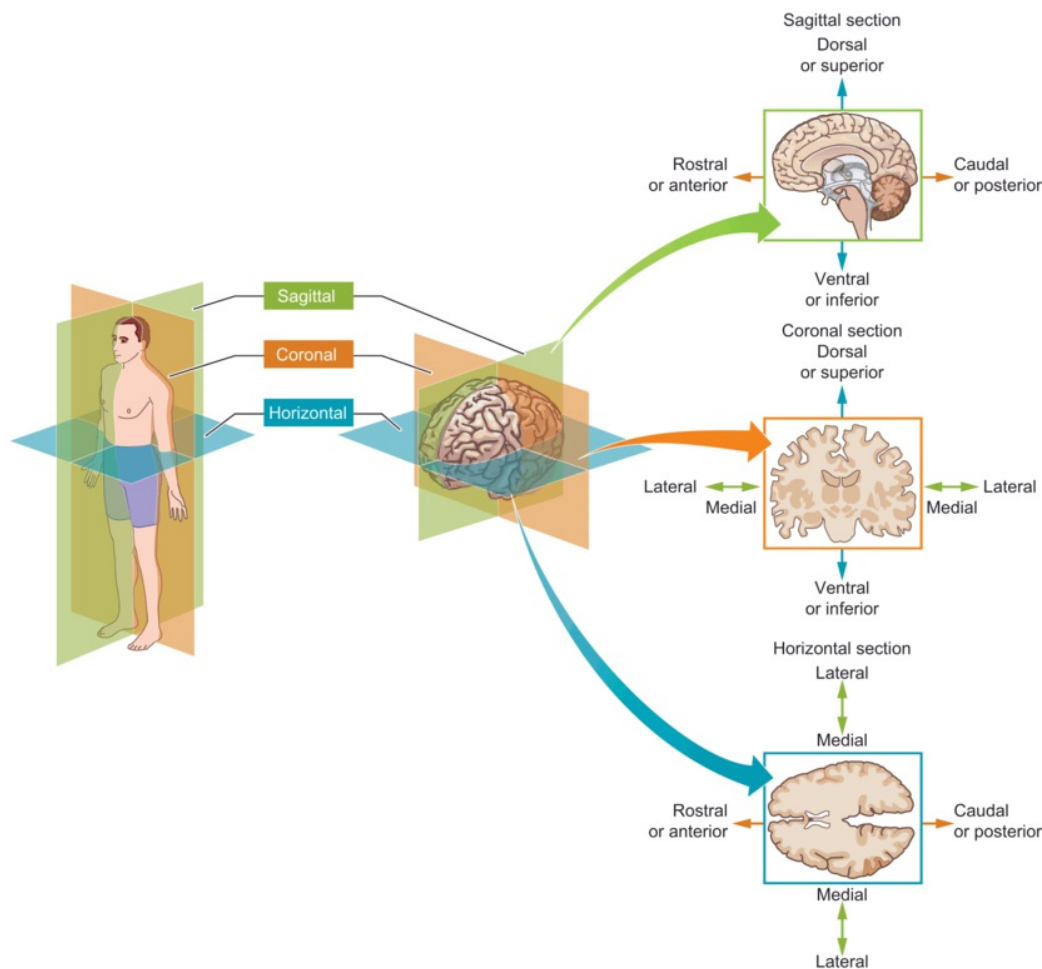


Figure 1.4 The main planes in which the brain is viewed.

A sagittal section divides left from right, a coronal section divides front from back, and a horizontal section divides top from bottom. The anatomical terms describing the brain as seen in each of these sections are shown on the right.

Knowledge of these terms can help us understand the location of specific brain structures. For example, when we are introduced to the anatomical structure called the lateral ventricle (a ventricle is a space within the nervous system that is filled with fluid), we can deduce that it must be positioned away from the midline of the brain (i.e., laterally). As another example, consider how we might go about locating **nuclei**, distinct groups of neurons whose cell bodies are all situated in the same region in a brain structure called the thalamus. As discussed later in this chapter, the thalamus helps to regulate and organize information coming from the outer reaches of the nervous system as it ascends toward the cortex. The thalamus also modifies information descending

from the cortex. If we need to find the anterior ventral nucleus of the thalamus, we know from our discussion of anatomical terms that it should be located at the front and bottom part of the thalamus.

Other terms we need to know include [contralateral](#), meaning on the opposite side, and [ipsilateral](#), meaning on the same side. So, for example, the left half of your brain is contralateral to your right hand, whereas it is ipsilateral to your left hand. To make these definitions more concrete, remember the familiar adage that the right side of your brain controls the motor movements of the limbs on the left side of your body, and vice versa. Put in the terms we just learned, motor control occurs contralaterally.

[Unilateral](#) applies to only one side of the brain, whereas [bilateral](#) applies to both sides of the brain. For example, when injury occurs to one side of the brain, it is unilateral damage, but when injury occurs to both sides, it is bilateral damage. Other terms often used to describe brain regions and their relation to body parts are [proximal](#), which means near, and [distal](#), which means far. Thus, distal muscles are in your far extremities, such as your hands.

Major Subdivisions of the Central Nervous System

We now start our journey across the different territories, or regions, of the [central nervous system \(CNS\)](#). The central nervous system encompasses the brain and the spinal cord, whereas the [peripheral nervous system](#) comprises all neural tissue beyond the central nervous system, such as neurons that receive sensory information or that send information to muscles, and those that relay information to or from the spinal cord or the brain. Because of its fragility, the entire central nervous system is encased in bone. The spinal cord is enclosed within the spinal column and the brain is enclosed within the skull. Although these bony structures protect the central nervous system, at times they can cause damage. For example, if the spinal column presses against the spinal cord, it

can pinch a nerve and cause pain. Likewise, as discussed in [Chapter 16](#), the brain can be damaged by compression against the skull.

Between the neurons and their bony encasements is [cerebrospinal fluid \(CSF\)](#), which is similar in composition to blood plasma. Essentially, the brain floats in CSF, which makes it buoyant and cushions it from being knocked around every time we move. The fluid-filled spaces that contain CSF are known as [ventricles](#), the most prominent of which are the lateral ventricles ([Figure 1.5](#)). CSF also serves metabolic needs, allowing nutrients to reach neurons. Typically, cells outside the nervous system receive nutrients from the blood. However, the blood–brain barrier precludes direct transport of nutrients from the blood to the brain. Rather, nutrients from the blood reach nerve cells through CSF.

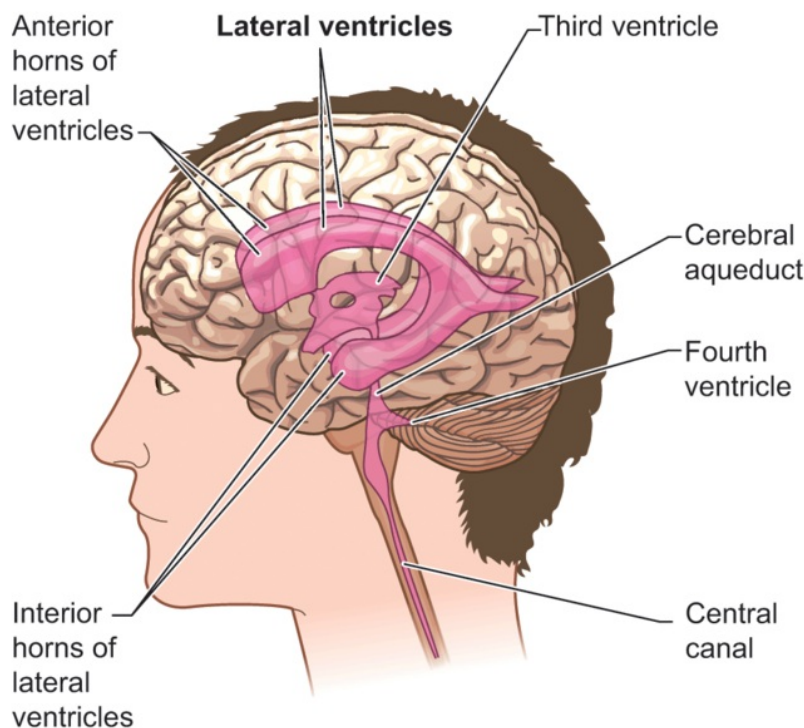


Figure 1.5 The ventricular system of the brain.

This system of spaces in the brain is filled by cerebrospinal fluid. It consists of the two lateral ventricles, one in each of the cerebral hemispheres, and the third and fourth ventricles positioned along the midline, which are connected via the cerebral aqueduct. The cerebrospinal fluid in the ventricles helps to cushion the brain and also aids in allowing nutrients to reach neurons.

Having discussed the basic organization of the nervous system, we now turn to examine the seven main subdivisions of the central nervous system depicted in [Figure 1.6](#): (1) the spinal cord, (2) the medulla, (3) the cerebellum, (4) the pons, (5) the midbrain, (6) the hypothalamus and thalamus (diencephalon), and (7) the cerebral cortex. In addition, we discuss two major subcortical systems, the basal ganglia and the limbic system.

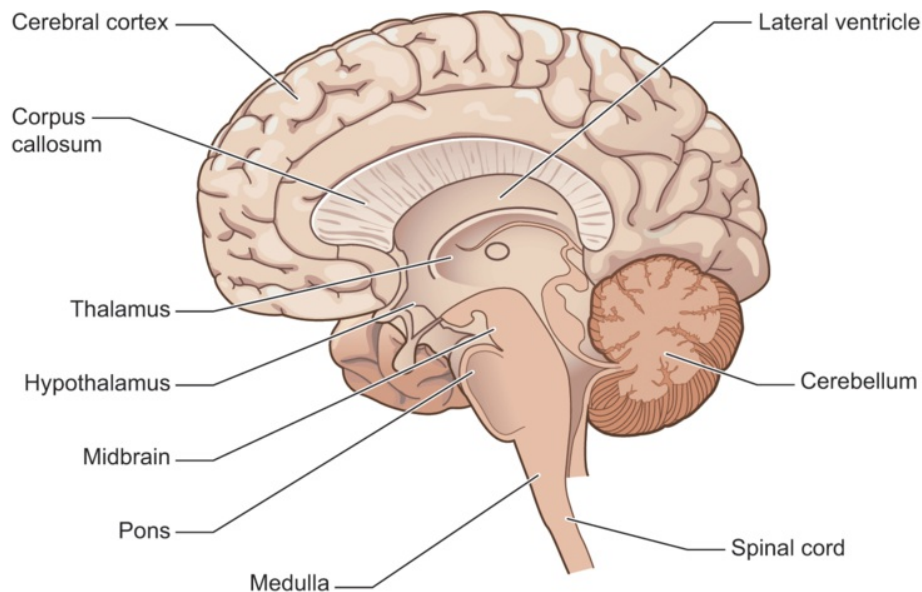


Figure 1.6 The major subdivisions of the human brain.

A sagittal view of the major subdivisions: the spinal cord, medulla, cerebellum, pons, midbrain, diencephalon (thalamus and hypothalamus), and cerebral cortex. The medulla, pons, and midbrain are often referred to as the brainstem. Sometimes the brain is conceived of as having three broad sections: the hindbrain (medulla, pons, and cerebellum), the midbrain, and the forebrain (diencephalon and cerebral cortex).

Spinal Cord

The [spinal cord](#) is the portion of the nervous system through which most sensory neurons relay information on the way to the brain, and through which motor commands from the brain are sent to the muscles. The spinal column, the bony structure housing the spinal cord, is composed of many sections, or vertebrae. At each vertebra, sensory information enters the cord and motor information leaves it. If the spinal cord were cut

in cross-section, two clumps of nerve cells, one located ventrally and another located dorsally, would be prominent, as shown in [Figure 1.7](#). Cells in the dorsal section of the spinal cord (remember, dorsal is located toward the back) receive sensory information. In contrast, cells in the ventral region (remember, ventral is located toward the stomach) are responsible for conveying motor commands to the muscles as well as receiving input from the brain and from other regions of the spinal cord.

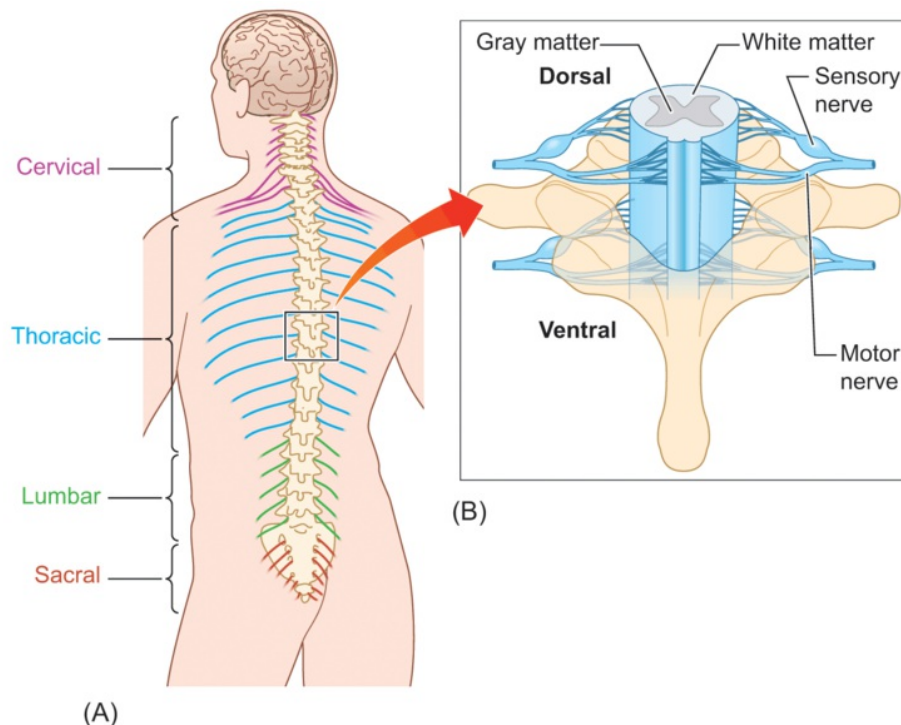


Figure 1.7 The spinal cord.

(A) The four sections of the spinal cord: cervical, thoracic, lumbar, and sacral. A spinal nerve exists at each vertebra of the spinal column. (B) A cross-section of the spinal cord. Sensory information enters the spinal cord through the dorsal region, and nerves exit through the ventral region to control muscle movements. The gray matter consists largely of cell bodies. The surrounding white matter is composed of myelinated axons that carry information to other levels of the spinal cord and the brain.

Damage to the spinal cord leaves a person without sensation in or motor control for all body areas that are connected to the brain by spinal cord segments distal to the point

of injury. Impulses from the periphery cannot be carried up the spinal cord past the point of injury and therefore cannot reach the brain. Likewise, information from the brain cannot be relayed down past the point of injury to the muscles. How much of the body is paralyzed and how much sensation is lost depends on where in the spinal cord the damage occurs.

The vertebrae where information from each part of the body enters the spinal cord are shown in [Figure 1.8](#). Compression of the spinal column that causes a vertebra to be broken or crushed may result in a damaged or severed spinal cord. For example, when damage to the spinal cord occurs at the level of the fifth cervical vertebra (C-5), the person is often left quadriplegic, without control of muscles in or sensation from either the arms or the legs (see [Figure 1.8](#)). If, however, the damage is sustained at a lower level, perhaps waist level (e.g., at vertebra T-12, the twelfth thoracic vertebra), the person is often paraplegic, with loss of sensory information and motor control for just the bottom half of the body.

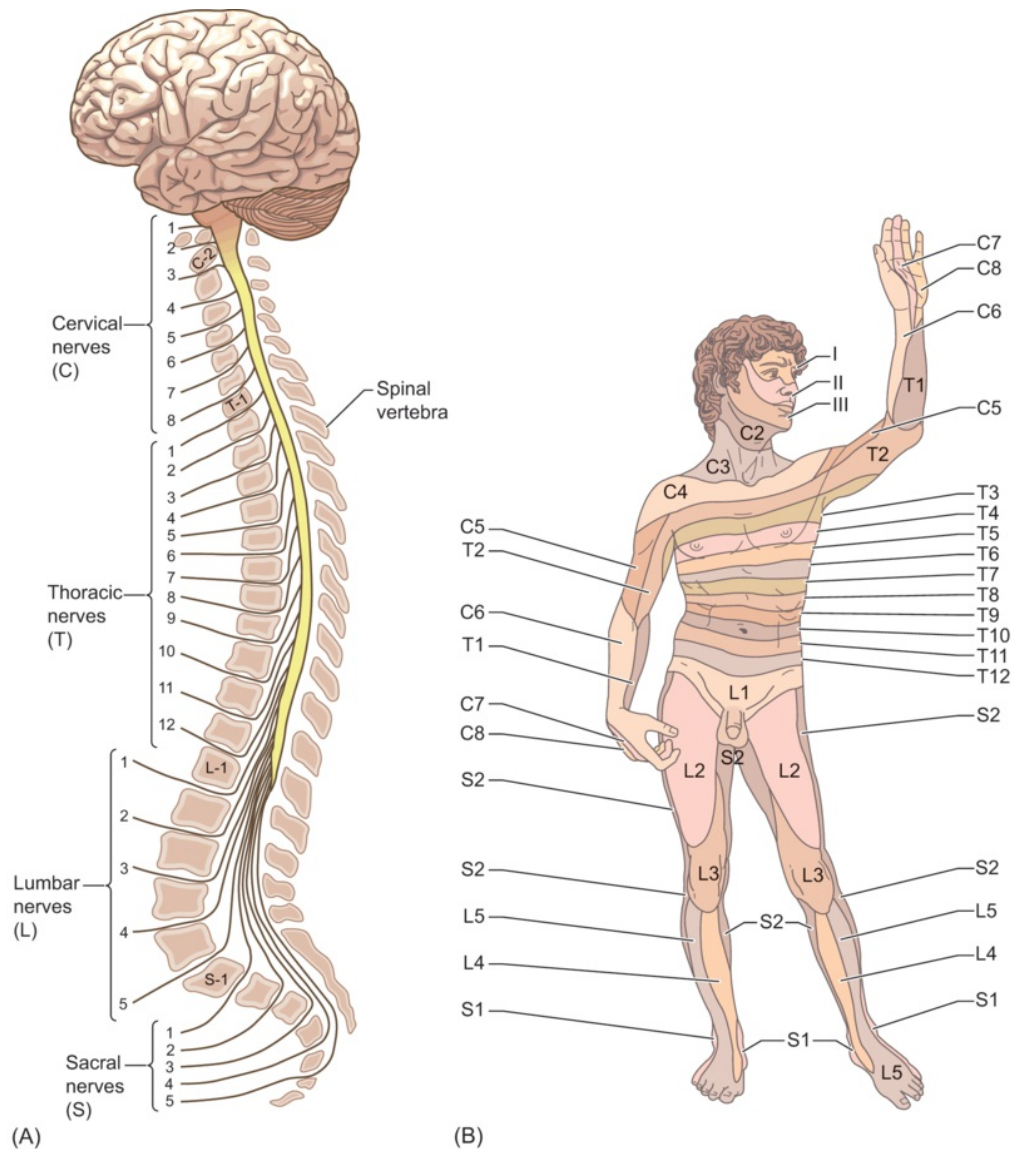


Figure 1.8 The location of the spinal nerves and the portions of the body they innervate.

(A) Shown on the left are the positions where each of the spinal nerves exits the spinal column. (B) On the right is a map indicating which sensory nerve carries information from that portion of the body to the spinal cord. Determining the locations of sensory loss after trauma to the spinal cord by using such maps helps medical personnel determine the level of the spinal cord at which the damage occurred. Information from the face reaches the brain via the cranial nerves.

Medulla: Control of Basic Functions

For the purposes of this text, we should know a few main facts about the [medulla](#), the section of the brain directly superior to the spinal cord. First, it is the region of the brain that contains many (though not all) of the cell bodies of the 12 [cranial nerves](#). Whereas the spinal cord is the point of entry and exit for sensory and motor nerves of the body, some cranial nerves are responsible for receipt of sensory information and motor control of the head. Other cranial nerves are responsible for the neural control of internal organs. A list of the 12 cranial nerves and their functions, and a diagram of the region of the brain where their nuclei are located, are presented in [Figure 1.9](#).

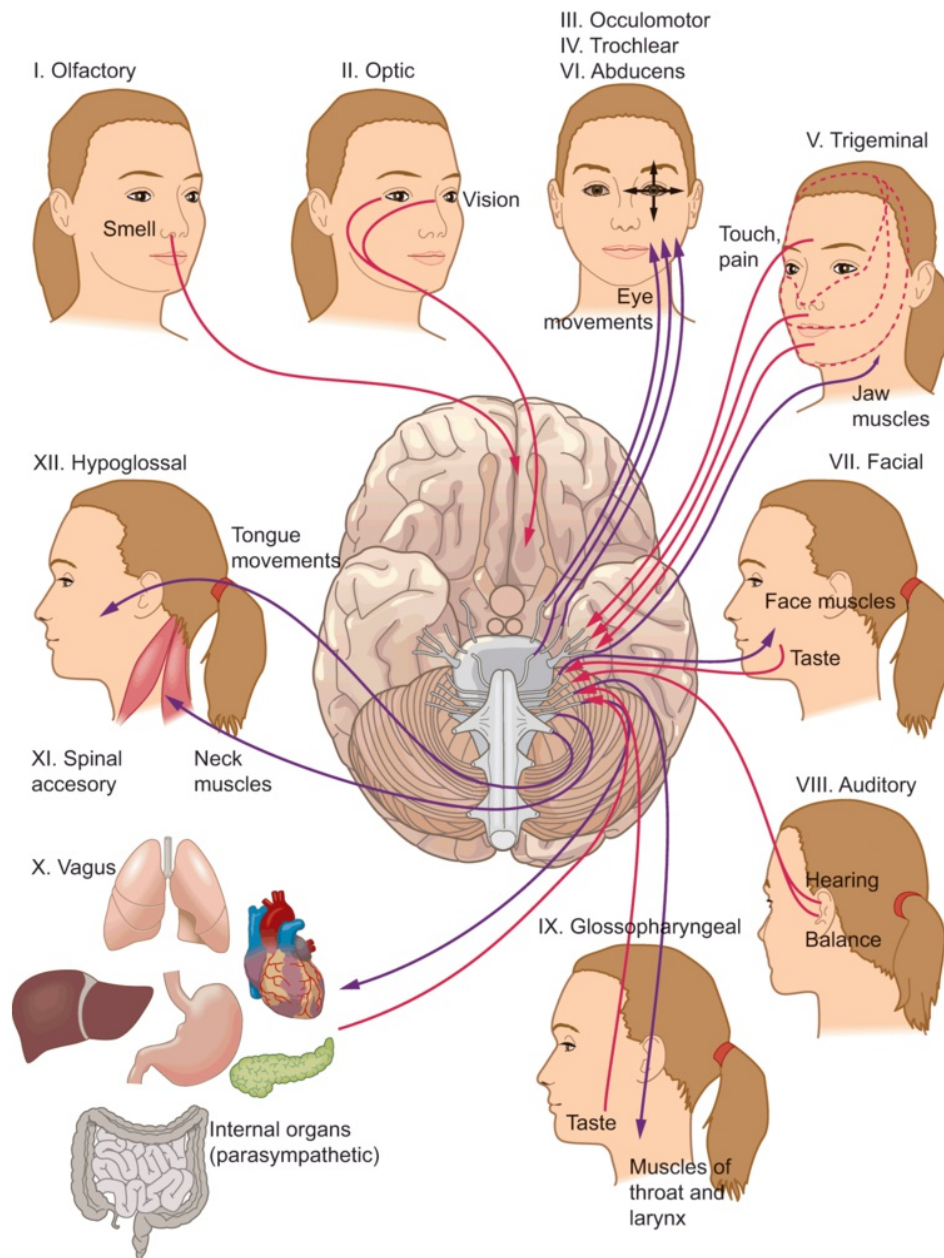


Figure 1.9 Locations at which the 12 cranial nerves enter or exit the brain, and each nerve's functions.

A ventral (bottom) surface view of the brain is shown in the middle. The majority of cranial nerves enter at the medulla and the pons. The magenta lines represent sensory functions; the purple lines show motor functions. Some cranial nerves are sensory only, some are motor only, and some are mixed.

Second, at the medulla, most of the motor fibers cross from one side of the body to the other, with the result that the left side of the brain controls the right side of the body,

and the right side of the brain controls the left side of the body. Third, the medulla controls many vital functions and reflexes, such as respiration and heart rate. Because the medulla serves these functions, damage to it can be fatal. One common accompaniment of either diffuse or specific brain damage is swelling of the entire brain. When this swelling puts enough pressure on the medulla to interfere with its functions, death can result.

Fourth, the medulla is home to part of a set of the neurons known as the [reticular activating system \(RAS\)](#). These neurons receive input from the cranial nerves and project diffusely to many other regions of the brain. The reticular activating system is important for overall arousal and attention, as well as for regulation of sleep–wake cycles. [Chapter 10](#) discusses this system in more detail.

Cerebellum: Fluid Movement

Located posterior to the medulla (see [Figure 1.6](#)) is the [cerebellum](#), a brain region important for the regulation of muscle tone and guidance of motor activity. In large part, it is the region of the brain that allows a pianist to play a piece of music seamlessly or a pitcher to throw a ball fluidly. Damage to the cerebellum does not result in paralysis, but instead interferes with precision of movement and disrupts balance and equilibrium. The classic test used to detect cerebellar damage is one in which the doctor asks a person to alternate between touching his or her own nose, and then the doctor's. Although a person with cerebellar damage can follow this command, the path taken by the hand from one nose to the other will be imprecise and jagged. Damage to the cerebellum also contributes to lack of balance and motor control. A common manifestation of temporary disruption to the cerebellum is seen in punch-drunk syndrome, in which an individual temporarily loses balance and coordination after sustaining a hard blow to the head.

Recent evidence suggests that a specific region of the cerebellum, the lateral cerebellum, may also be linked to certain aspects of cognitive processing, allowing for fluidity and precision in mental processes (Stoodley, [2012](#)). The lateral cerebellum may

also be critical for the timing of discrete temporal intervals, acting as the brain's internal clock (Breska and Ivry, [2016](#)).

Pons: A Connective Bridge

Directly superior to the medulla and anterior to the cerebellum, we find the multifunctional **pons** ([Figure 1.10](#)). Because of its anatomical location, it acts as the main connective bridge from the rest of the brain to the cerebellum, and as the point of connection between most of the cranial nerves and the brain. The pons also acts as an important center for the control of certain types of eye movements and for vestibular functions (e.g., balance). Finally, the pons is the site of the superior olive, one of the points through which auditory information is relayed from the ear to the brain. At the superior olive, information from both ears converges, allowing comparison of the information received from each ear. Such comparison is thought to be important for localization of sounds (see [Chapter 5](#)).

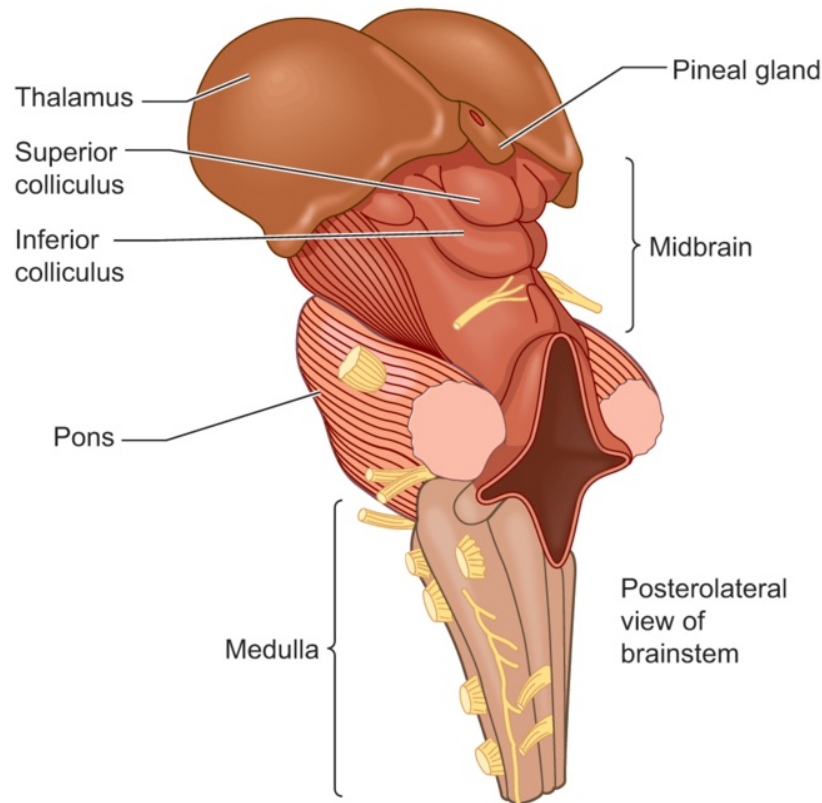


Figure 1.10 Brainstem, including medulla, pons, and midbrain.

The brainstem is a region of the brain that is important for relaying information to and from the cortex.

Midbrain: Orienting by Sound and Sight

Superior to the pons lies the [midbrain](#) (Figure 1.10). Like the pons and medulla, this region of the brain contains the nuclei of the cells that form some of the cranial nerves. The midbrain also contains two important structures on its dorsal side, the [inferior colliculus](#) and the [superior colliculus](#), which play a role in orienting us to stimuli in the auditory and visual modalities, respectively (Figure 1.10).

Like the superior olive, the inferior colliculus is a relay point for auditory information as it travels from the ear to the cortex; thus, it appears to be involved in sound localization. However, it also contributes to reflexive movements of the head and eyes in response to sound, which provide us with the rudimentary ability to orient

toward salient auditory stimuli. The superior colliculus is the visual system's equivalent of the inferior colliculus, allowing us to perceive and orient toward large moving objects in the periphery. In [Chapters 5](#) and [10](#), we revisit the role of the superior colliculus in orienting toward visual information and guiding the eyes toward spatial locations or objects of interest.

Hypothalamus: Maintaining the Body's Equilibrium

The general role of the [hypothalamus](#) ([Figure 1.11](#)) is to control behaviors that help the body satisfy its needs so it can maintain equilibrium. When organisms have a particular need, they generally emit a behavior designed to bring the body back to a stable state, known as homeostasis. For example, when hungry or thirsty, a person will engage in behaviors that lead to ingesting food or drink; if cold, the person will search for a blanket or a warmer location. The hypothalamus provides the signals telling the brain that these sorts of behaviors are needed.

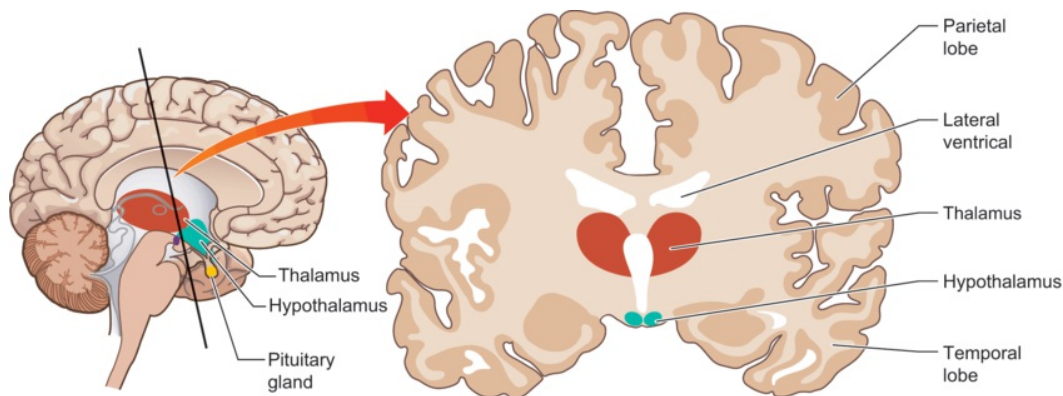


Figure 1.11 The diencephalon.

The diencephalon is comprised of the hypothalamus and the thalamus. The hypothalamus is involved in controlling behaviors so the body can maintain its equilibrium. It does so, in part, by its connections with the hormonal system, in particular the pituitary gland. The thalamus is a major relay point for information going to and coming from the cortex. The slice shows the position of the structures that form the diencephalon in relation to the lateral ventricle above it and regions of the cerebral cortex surrounding it.

Let's now examine the role of the hypothalamus in each of a variety of such functions in more detail. One of the main functions of the hypothalamus is to aid in feeding and drinking behavior. For example, research with animals has demonstrated that damage to the ventromedial region of the hypothalamus causes an animal to eat more than is required to maintain a normal body weight; such behavior eventually leads to obesity. Likewise, lesions (wounds, damage, or injuries) to dorsal and lateral regions of the hypothalamus can interfere with water intake. Another main function of the hypothalamus is to aid in regulation of body temperature. Some neurons in both anterior and posterior sections of the hypothalamus detect changes in the temperature of the skin or blood and therefore function like a thermostat.

The hypothalamus also has an intimate relationship with the hormonal system, which is the system that releases chemical messengers to be carried throughout the body by means of the bloodstream, so as to exert their influence on target organs far from their point of production. The hypothalamus either secretes hormones itself or produces other factors that regulate activity of additional brain regions that secrete hormones. The connections of the hypothalamus with the pituitary gland are an example of the latter. This linkage of the hypothalamus to the hormonal system helps explain its role in sexual behavior, daily (diurnal) rhythms, and fight-or-flight reactions. These aspects of behavior are most relevant to our discussion of emotion in [Chapter 12](#).

Thalamus: Gateway to the Cortex

Along with the hypothalamus, the [thalamus](#) (see [Figure 1.11](#)) is part of the [diencephalon](#). It is a large relay center for almost all sensory information coming into the cortex and almost all motor information leaving it. A [relay center](#) is a brain region in which the neurons from one area of the brain synapse onto neurons that then go on to synapse somewhere else in the brain. Often, the pattern of connections between neurons at relay centers serves to reorganize information before it is sent elsewhere in the nervous system.

To give you a better sense of how certain brain regions, including the thalamus, act as relay centers, consider an analogy to the distribution of eggs laid by a group of chickens, each of which has a particular roost. In this case, eggs, rather than information, are being relayed from one point to another. Initially, each hen lays a set of eggs in her nest. These eggs are then sent down the conveyor belt toward the processing plant in a systematic order so that eggs laid by hens with roosts next to each other end up on the belt next to each other. However, as the eggs reach the plant, they are sorted into two piles on the basis of size; therefore, all the small eggs are packaged together and all the large ones are packaged together. Such a system preserves basic information about life in the henhouse (because eggs from hens with adjacent roosts get packaged next to each other), but nonetheless also sorts the information in a novel way (because the eggs are now segregated with regard to size).

The connections of the thalamus are extremely complicated, and understanding all of them could be a course (and textbook) unto itself. For our purposes, remember that the patterns of connections, both to and from the thalamus, are very specific. One particular region of the thalamus receives information from just one sensory system and projects to only one particular region of the cortex. This organization is much like a train station, where trains coming and going from certain locations tend to come in and leave on specific tracks.

Major Subcortical Systems: The Basal Ganglia and the Limbic System

Two important neural systems reside mainly within regions of the midbrain and diencephalon: the basal ganglia, important for motor control, and the limbic system, important for emotions. Because many or all the structures in these systems are located in regions below the cerebral cortex, they are referred to as subcortical systems.

The [basal ganglia](#) consist of the caudate nucleus, the putamen, the globus pallidus, and nucleus accumbens, all of which are structures located near the thalamus ([Figure 1.12](#)). Degeneration or destruction of these areas leads to difficulty in motor control, generally characterized by involuntary movements. Damage to the globus pallidus leads

to involuntary twisting and turning of the limbs. In contrast, damage to the caudate nucleus and putamen causes involuntary movements, such as tremors while the person is at rest, as well as the introduction of extra movements into a standard progression of voluntary movement such as walking. [Chapter 4](#) discusses the role of these structures in motor behavior in much more detail.

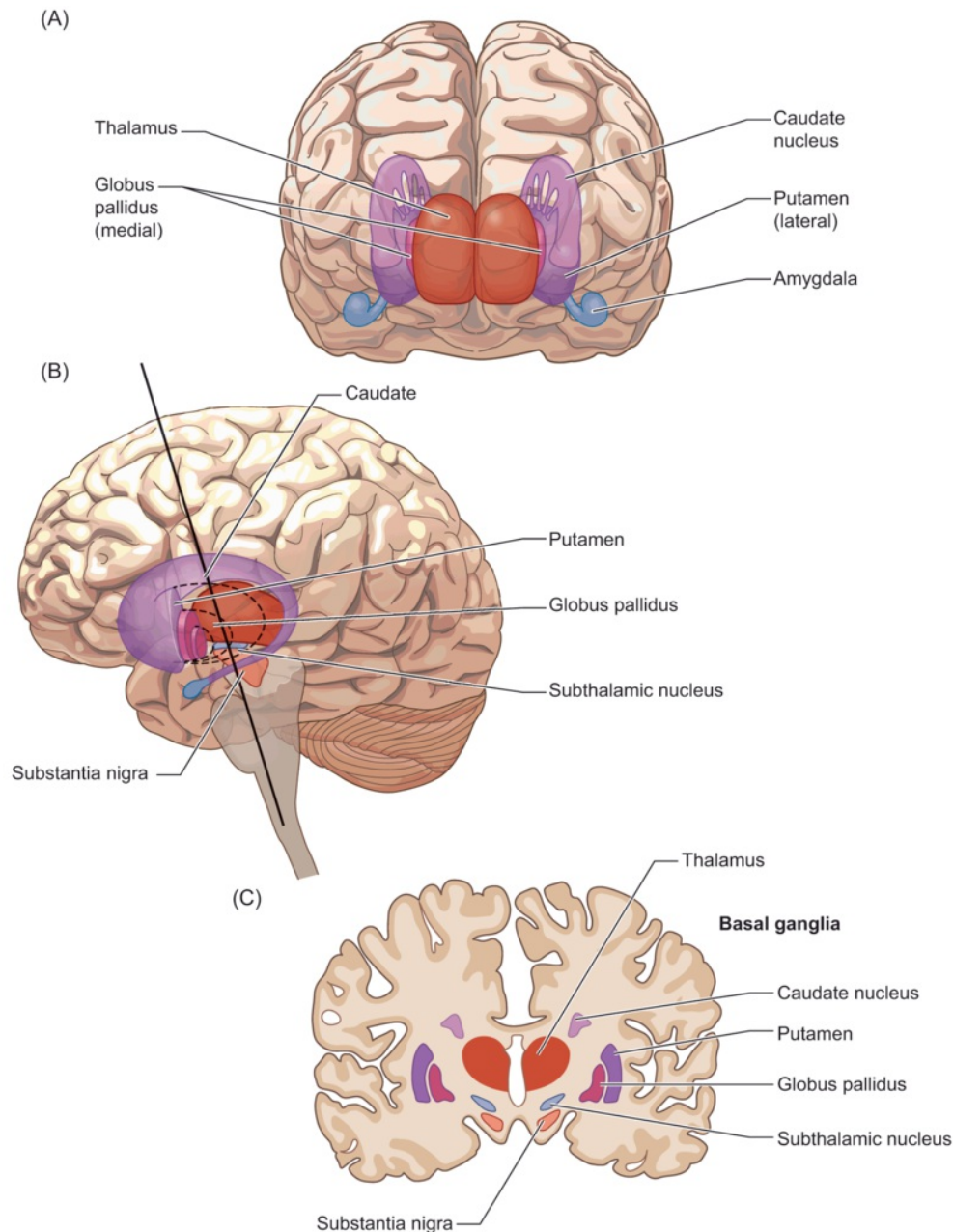


Figure 1.12 The location of basal ganglia deep within the brain.

(A) View from the front of the brain, (B) view from the side and (C) coronal view. The basal ganglia are comprised of the globus pallidus, the caudate nucleus, and the putamen. Notice how they are located lateral to the thalamus. Also note that the head of the caudate nucleus is anterior and that this structure wraps around to its tail, which is located next to the amygdala.

The [limbic system](#) is a series of subcortical structures that were initially believed to be a circuit for integrating emotional information between various parts of the nervous

system. Scientists thought that these structures functioned mainly to process emotional information, by linking information from the sensory world and from an individual's internal state with information from the cortex. Although the general concept of the limbic system has been retained, we know now that the structures forming the limbic system play a much more complicated role in a variety of functions.

Limbic structures include the amygdala, the hypothalamus, the cingulate cortex, the anterior thalamus, the mammillary body, and the hippocampus ([Figure 1.13](#)). We discuss the roles of these structures in more detail in later chapters. For example, the amygdala has been implicated in the quick response to salient emotional information, as discussed in [Chapter 12](#). The hippocampus plays an important role in memory, specifically the formation of new long-term memories, as described in [Chapter 9](#), and the cingulate cortex has been implicated in the selection of actions as well as the motivation to make those actions, as discussed in more detail in [Chapters 4](#) and [11](#) respectively.

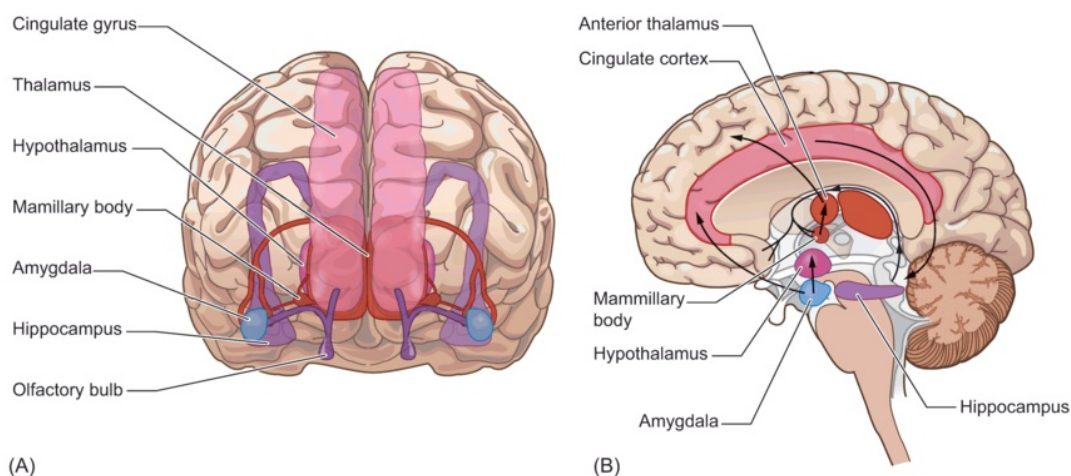


Figure 1.13 The structures that constitute the limbic system.

The limbic system consists of the amygdala, the mammillary body, the cingulate cortex, the anterior thalamus, the hippocampus, and the hypothalamus. (A) The position of the limbic structures deep within the brain. (B) A diagram of the connectivity between different limbic regions illustrating how they form a system.

Cerebral Cortex

The cerebral cortex is the region that most often comes to mind when we think of the brain (see [Figure 1.6](#)). The cortex plays a primary role in most of the functions discussed in the remainder of this text, such as object recognition, spatial processing, and attention. The cortex is divided into two physically separated halves, each called a [cerebral hemisphere](#). Although at first glance these two hemispheres look similar, we learn in [Chapter 2](#) that they differ in both function and anatomy.

Each convolution, or bump, of the brain is called a [gyrus](#) (plural: gyri) and is basically a giant sheath of neurons wrapped around the other brain structures just discussed. These convolutions serve to pack more brain tissue into a smaller space, much as rolling your clothes allows you to get more of them into your suitcase. Each valley between the bumps is called a [sulcus](#) (plural: sulci), and if it is deep it is known as a [fissure](#).

Every brain has the same basic gyral pattern, just as every face has the same basic pattern (i.e., eyes above the nose, mouth below the nose). However, subtle individual variations exist in the gyral pattern, just as facial configuration varies (e.g., some people have wide-set eyes, whereas in others the eyes are close together). The major gyri and sulci of the brain and their names are shown on the inside front cover of your book ([Figures A–D](#)). You can use these diagrams as reference as you work your way through the rest of the book.

Three major fissures serve as prominent landmarks in the brain because they help in conceptualizing distinctions in function between major brain regions. The first of these is the [central fissure](#), sometimes called the Rolandic fissure, which separates each hemisphere of the brain in an anterior–posterior dimension. In general, areas of the brain in front of the central fissure are more involved in motor processing, whereas those behind are more involved in sensory processing. The second major fissure is the [Sylvian \(lateral\) fissure](#), which separates each hemisphere of the brain in the dorsal–ventral dimension. This division (sometimes alternatively called the fissure of Sylvius) is important because the area of the brain below the Sylvian fissure is the

temporal lobe, which plays a key role in memory, emotion, and auditory processing. The third major fissure is the [longitudinal fissure](#), which separates the right cerebral hemisphere from the left. This division is important because each hemisphere has a unique specialization with regard to both cognitive and emotional functioning.

These three major fissures also divide each hemisphere into four major regions, or lobes. The area in front of the central fissure is known as the [frontal lobe](#). The area below the Sylvian fissure is the [temporal lobe](#). The region directly behind the central fissure but above the Sylvian fissure is the [parietal lobe](#). The remaining region of the brain behind the parieto-occipital sulcus is the [occipital lobe](#) (see [Figure 1.22](#)). We will return to the four major lobes of the brain later in this chapter, after we first zoom in to examine neurons themselves in more detail.

A Closer Look at Neurons

The structure and function of neurons allows them to convey information across various points in the nervous system. In this section, we review the fundamentals of neural signaling and learn about specific neuronal subsystems that differ in the particular chemicals they use to convey information.

Electrochemical Signaling in the Nervous System

Neurons transfer information by means of a combination of electrical and chemical processes. There are two broad principles to this electrochemical signaling: information is relayed within a neuron by means of an electrical signal, whereas one neuron influences another via a chemical signal.

How Information Is Transferred Within a Neuron

To better understand these principles, we need to know that at rest, there is a difference in the electrical charge between the inside and outside of the neuron. This is known as the neuron's [resting potential](#), and typically is about -70 millivolts (mV). It occurs

because the cell membrane of the neuron acts as a barrier separating ions, which are electrically charged particles, on the inside from those on the outside. Ions, such as sodium and potassium, can traverse the cell membrane only through special passageways known as an ion channel. In some configurations they allow ions to flow in and out of the cell, and in other configurations, the passageway is blocked and ions cannot move from one side of the cell membrane to the other.

Input from other neurons can affect the opening and closing of ion channels. The resulting change in the ion concentrations on each side of the membrane drives the neuron's electrical charge away from its resting potential, making it either more negative or more positive. If the cell receives enough stimulation to reduce the voltage across the membrane to about -55 mV, a threshold is passed and the cell "fires." When a cell fires, the electrical charge of the neuron reverses quite rapidly from -55 mV to a peak of $+40$ mV. After reaching the peak – a state known as depolarization – the electrical charge then retreats toward the baseline resting potential, which is known as repolarization. The voltage then briefly becomes even more negative than the resting potential, a phase known as hyperpolarization. Following hyperpolarization, the neuron returns to the resting potential. The whole sequence of events just described, from resting potential and back again, is known as an **action potential** (see [Figure 1.14](#)).

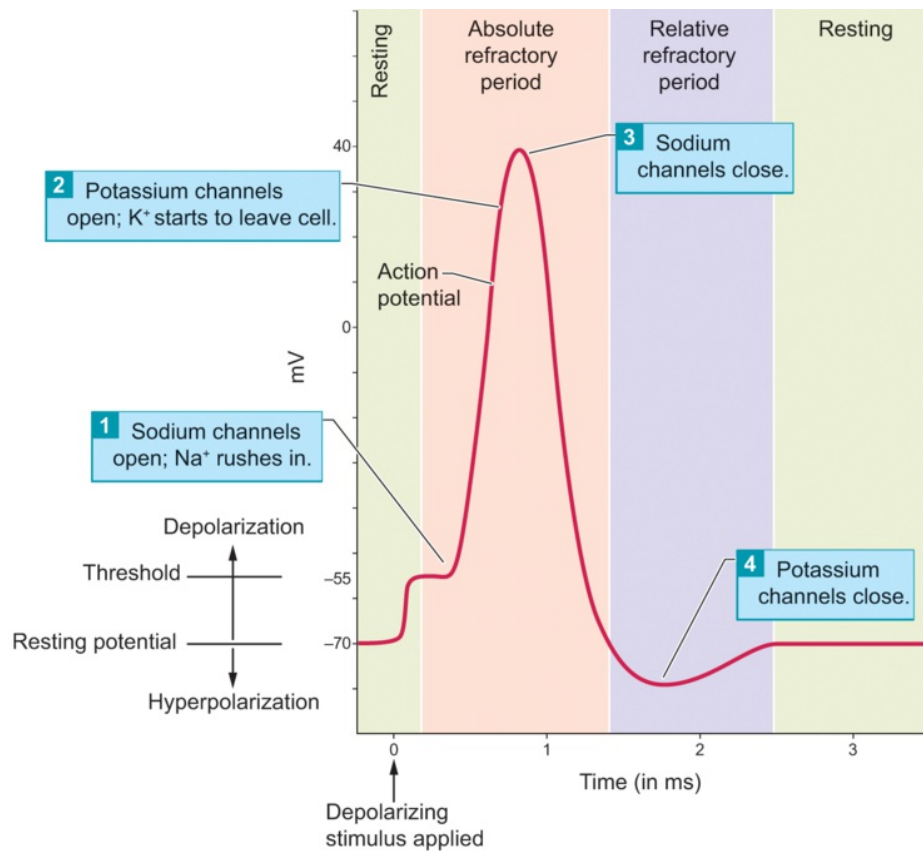


Figure 1.14 Phases of the action potential.

(1) When the threshold of activation is reached, sodium (Na⁺) begins to enter the cell. (2) Potassium (K⁺) begins to leave the cell. (3) No more sodium enters the cell, and the voltage reaches its peak positive value. (4) The leakage of potassium drives the voltage in the negative direction, hyperpolarizing the cell; potassium channels then close and the cell returns to its resting potential.

This action potential has three very important properties. First, it is self-propagating, which means that once it is set in motion nothing else need be done – much as knocking down one domino causes all the others in a line to fall as well. Second, its strength does not dissipate with the distance that it travels. The peak of the action potential remains +40 mV for its entire trip down the axon. In this characteristic it is quite unlike sound, for example, which loses energy the further it travels. Third, the action potential is an all-or-nothing response: either the cell “fires” (i.e., has an action potential) or it doesn’t.

[Figure 1.15](#) shows the main parts of a neuron in detail, while [Figure 1.16](#) shows the basics of neural transmission. The action potential is first produced at a specific part of the neuron near the cell body called the [axon hillock](#). From there, the action potential is carried along the entire length of the axon to the terminal bouton, which is the end of the road for the action potential. Here the electrical signal gets transformed into a chemical message. The terminal bouton contains little balloons, known as [synaptic vesicles](#), which are filled with neurotransmitter. Some of these synaptic vesicles reside in the bouton, whereas others are fused to the outside wall of the neuron. The action potential causes synaptic vesicles that are fused to the outside walls of the neuron to burst open, pouring their contents into the area between neurons known as the synaptic cleft. Once out of the vesicles, neurotransmitter molecules diffuse across the cleft into the vicinity of the neighboring neuron. The side of the cleft that releases the neurotransmitter is known as the presynaptic side; the opposite side, containing the outside edge of the neighboring neuron, is known as the postsynaptic side. This region of contact between the neuron containing the terminal bouton, the synaptic cleft, and the postsynaptic region is called a [synapse](#).

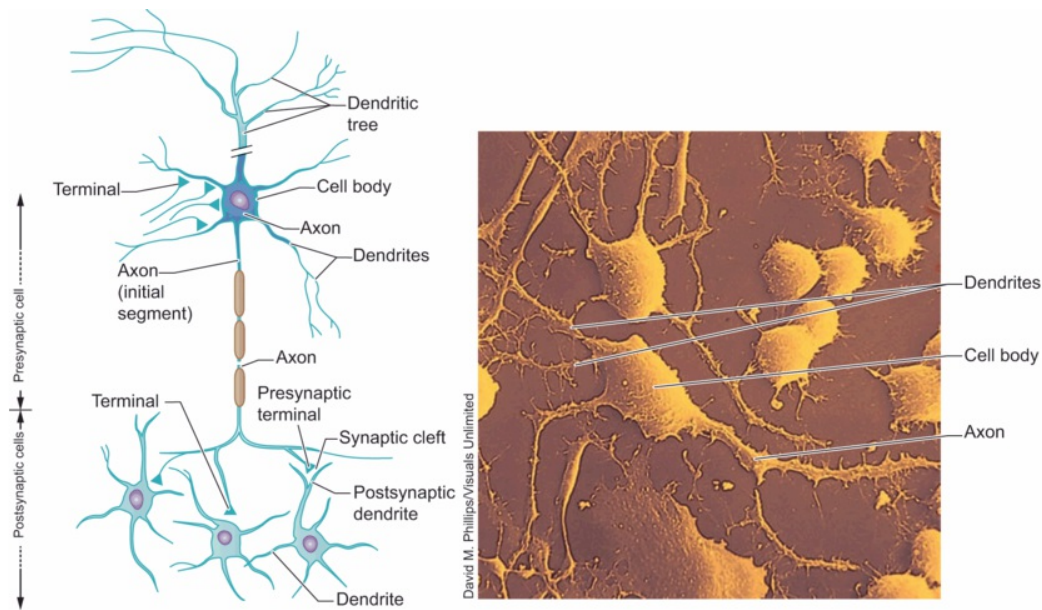


Figure 1.15 Basic parts of a neuron.

The dendritic tree, made up of individual dendrites, is the main region that receives information from other cells. The cell body contains the nucleus and the machinery necessary to support basic cell functions. The axon hillock is the location at which a large electrical signal is generated, and the axon is the long shaft of the cell across which this large electrical signal is propagated. The branches at the end of the axon contain bulbous-shaped terminals (terminal boutons or simply boutons), which have vesicles filled with neurotransmitters. These neurotransmitters, which can be either inhibitory or excitatory, are released into the space between adjacent neurons, which is known as the synaptic cleft. The neuron on the terminal side of the cleft is known as presynaptic and the neurons on the opposite side are referred to as postsynaptic. Some synaptic connections are made onto postsynaptic dendrites, whereas others are made directly onto the postsynaptic cell body. An axon can have many branches, synapsing with as many as 1,000 other neurons.

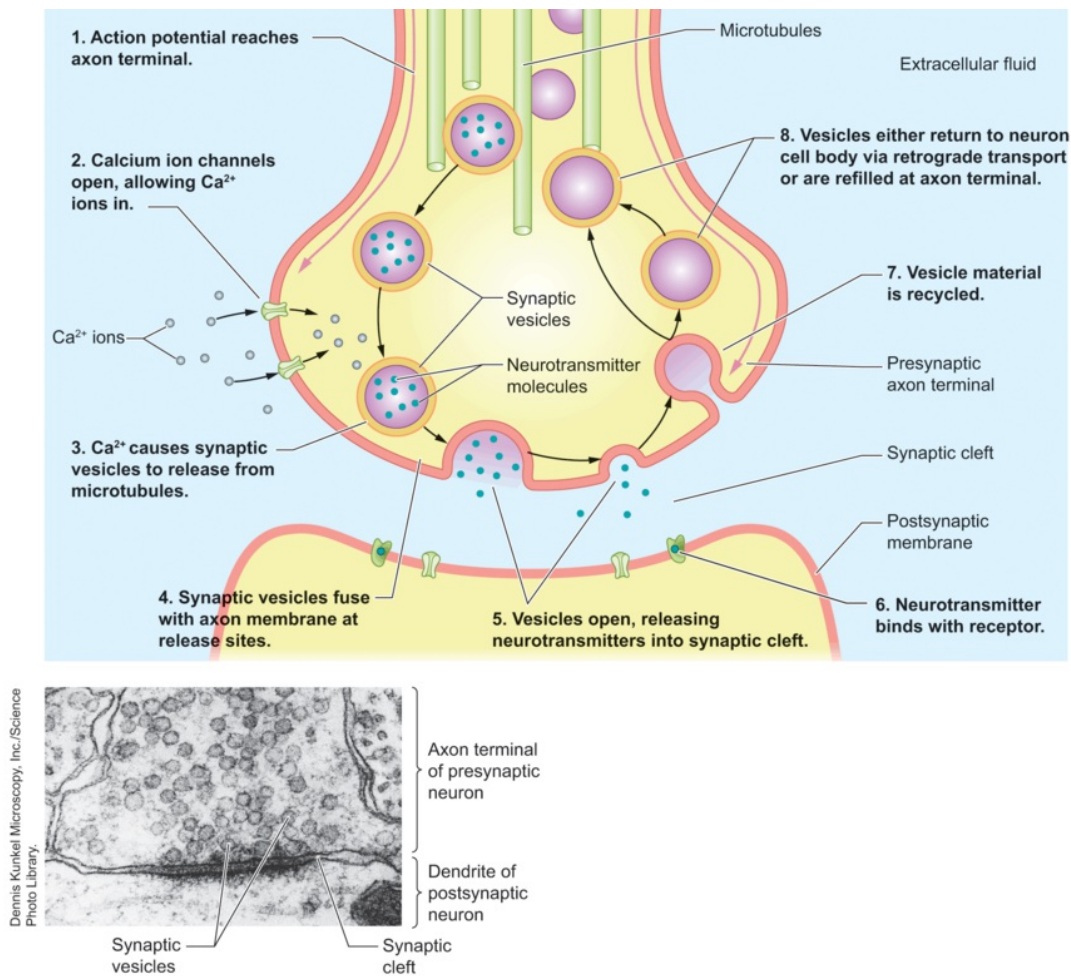


Figure 1.16 Important elements of neural transmission.

Within the presynaptic neuron are synaptic vesicles that contain molecules of neurotransmitter. When an action potential occurs, the neurotransmitter is released into the synaptic cleft through the steps depicted here. The neurotransmitter then binds with a receptor on the postsynaptic membrane, causing a local change in electrical voltage.

How Information Is Transferred Between Neurons

At the synapse, **neurotransmitter** molecules are released from the presynaptic neuron and received by the postsynaptic neuron. The membrane of the dendritic trees of the postsynaptic neuron contains regions known as **receptors**. These receptors are specially configured proteins that are embedded within the postsynaptic membrane. As shown in [Figure 1.16](#), when a neurotransmitter reaches the postsynaptic membrane, it fits into a

specific region of the receptor (called the binding site), much the way a key fits into a lock. The binding of the neurotransmitter changes the configuration of the receptor, which in turn changes the electrical charge of the postsynaptic neuron in a small local area near the receptor site by altering the flow of ions across the membrane. At this point, the chemical signal is transformed back into an electrical one.

How Postsynaptic Potentials Can Cause an Action Potential

The local changes in the electrical potential that occur near the receptor sites can make the electrical charge of the cell either more positive or more negative than the resting potential. An [excitatory postsynaptic potential \(EPSP\)](#) makes the cell's electrical charge a bit more positive – that is, it reduces the difference in electrical charge between the inside and the outside of the cell. This reduction brings the differential closer to the threshold value of -55 mV at which the cell will fire. In contrast, an [inhibitory postsynaptic potential \(IPSP\)](#) makes the inside of the cell a bit more negative than the outside and moves the cell further away from the threshold at which it will fire. Whether a particular neurotransmitter has an excitatory or inhibitory effect depends not on the neurotransmitter but rather on the receptor class to which it binds. We will talk a bit more about the many different classes of receptors later in this chapter.

Postsynaptic potentials differ from action potentials in three important ways. First, they are graded: The further they travel from their source, the more they dissipate. Thus, unlike the action potential, which remains constant for the entire course of its journey, postsynaptic potentials weaken as they travel across time and space. Second, postsynaptic potentials are much smaller in magnitude than an action potential, usually in the range of 0.5 to 5 mV. Third, whereas action potentials are always “excitatory,” in that they make the cell fire, postsynaptic potentials can be either excitatory or inhibitory.

Because postsynaptic potentials are small and dissipate over space, a single one of them is highly unlikely to cause a cell to fire. Rather, it requires the combined effect of

these potentials, both across time and across space, to make a neuron fire. For example, two EPSPs have a greater influence if they occur close together in time than if a gap in time separates them. Likewise, if two EPSPs occur at the same part of the dendritic tree, they are likely to have a larger influence than if they occurred in spatially disparate regions of the dendrite. You can appreciate the complexity of this summation process if you consider that the average neuron has hundreds to thousands of other neurons synapsing upon it. Thus, whether a single cell fires depends not on a single voice from a neighboring neuron, but rather on the chorus of EPSPs and IPSPs produced by its neighbors and on whether those voices occur close together in time and space.

The cacophony of postsynaptic potentials is summated at the axon hillock. If the summed value of EPSPs and IPSPs manages to change the differential in charge across the membrane at the axon hillock from its resting potential of -70 mV to around -55 mV, the cell will fire. If this value is not reached, the cell will not fire. Because the postsynaptic potentials are graded and lose their potency as they travel from their source to the axon hillock, potentials generated close to the axon hillock have a larger influence on whether or not the cell fires. Consequently, if we go back to our chorus analogy, the cells that synapse closer to the axon hillock have a louder voice in the chorus than those that synapse further away. In general, excitatory synapses are located on a dendritic tree, whereas inhibitory synapses are located on the cell body. Therefore, IPSPs are more likely to be generated closer to the axon hillock, where they can have a greater effect.

Because the value of the action potential is always the same, neurons cannot code the intensity of a stimulus by the size of its electrical response. Rather, neurons code the intensity of a stimulus via the rate, or pace, of its firing. When there is a strong stimulus, the cell fires many times in succession; when there is a weak input, it fires only occasionally (see [Figure 1.17](#)).

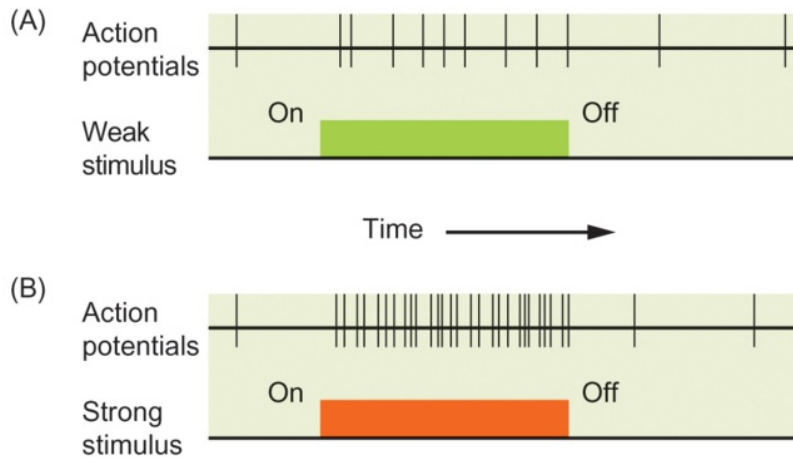


Figure 1.17 Neurons code the strength of a stimulus by the rate of firing.

(A) When a relatively weak stimulus is encountered, the cell fires relatively infrequently. (B) When a strong stimulus is encountered, the cell fires many times.

To better understand this concept, let's imagine you are taking pictures of various people and scenes. Consider a situation in which you find a person or vista interesting – you snap a picture or two. But what happens when you find someone overwhelmingly attractive or a vista breathtakingly beautiful? You snap lots and lots of pictures. Likewise, neurons code their “interest” in a stimulus by how many times they fire.

Factors That Modulate a Neuron's Response

The responsiveness of a neuron can be modulated in a number of manners. Many of the examples we provide are for the neurotransmitter [acetylcholine](#) (ACh), which is the chemical used in neurons that synapse onto muscles. When the neuron fires, it causes the muscle tissue to contract. Knowing this will help you appreciate some of the following examples. There are three main ways of modulating neurotransmission: by affecting presynaptic mechanisms, by modulating the amount of neurotransmitter in the synaptic cleft, and by affecting postsynaptic mechanisms.

There are three main presynaptic mechanisms for modulating a neuron's response. One way is to regulate the amount of neurotransmitter that is actually produced. For example, eating food rich in choline, such as cauliflower and milk, helps to promote the production of acetylcholine. Another way is to modulate the release of the

neurotransmitter into the synaptic cleft. For example, the venom of the black widow spider promotes the release of ACh, allowing it to flood the synaptic cleft. Because the excessive amount available keeps a large amount of ACh bound to the postsynaptic receptors, the person cannot initiate any other motor actions, becomes paralyzed, cannot breathe, and dies. Finally, [autoreceptors](#) located on the presynaptic neuron can bind the same neurotransmitter released by that neuron, which in turn decreases the activity of the presynaptic neuron. These autoreceptors work as a negative feedback mechanism, providing a way to keep the cell from becoming overactivated or overstimulated.

Likewise, a variety of mechanisms can modulate the amount of neurotransmitter in the synaptic cleft ([Figure 1.18](#)). One way is to affect reuptake mechanisms. For example, cocaine blocks reuptake of the neurotransmitter [dopamine](#), thereby causing stimulatory effects. Another way to modulate the amount of neurotransmitter is to inhibit the action of the enzymes that break them down. For example, insecticides, nerve gases, and herbicides all serve to inhibit [acetylcholinesterase](#), allowing ACh to accumulate in the synaptic cleft, eventually leading to neuromuscular paralysis. Notice that the end result here is similar to that observed with black widow spider venom. Both nerve gases and black widow spider venom have the same result: they lead to an excess of ACh. However, the mechanism by which this excess ACh is produced is different.

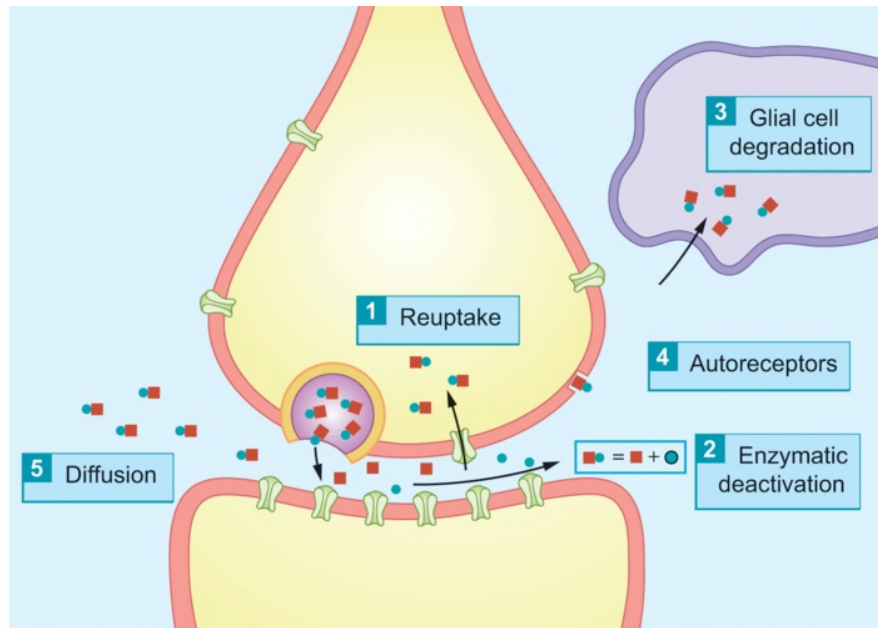


Figure 1.18 Mechanisms for modulating the amount of neurotransmitter in the synaptic cleft.

(1) Neurotransmitter may be taken up by the presynaptic neurons via special transporter molecules. (2) The neurotransmitter may be broken apart by enzymatic deactivation. (3) Glial cells may take up and destroy neurotransmitter. (4) Neurotransmitter may bind to an autoreceptor. (5) Neurotransmitter may diffuse away from the synapse.

The final major way to modulate neuronal activity is via postsynaptic mechanisms. One set of mechanisms affects the binding of the neurotransmitter with the receptor. A drug can increase activity by mimicking the effect of a neurotransmitter, thus serving as an agonist. For example, the physical structure of nicotine is similar enough to that of acetylcholine to allow it to fit into the binding sites of the postsynaptic receptor and be effective in opening the ion channels. Thought of this way, an agonist is like an alternative key that can open the lock. In contrast, a drug may block postsynaptic sites, precluding the neurotransmitter from doing so, and thereby act as an antagonist. For example, because it occupies the receptor site, curare prevents acetylcholine from binding postsynaptically. Yet, when in the receptor site, curare does not open the ion channel. Its action is much like having a key that fits in a lock but can't turn there. It is

just jammed in the lock, preventing the correct key from being used. This jamming of the lock mechanism explains why curare causes paralysis: Acetylcholine cannot bind with the receptor to produce muscle activity.

Another set of mechanisms influences how long the neurotransmitter is bound to the receptor, so that the postsynaptic receptors are freed for another influx of neurotransmitter, which can then produce IPSPs or EPSPs. This can occur either by [reuptake](#), which is the rapid removal of neurotransmitter back into the terminal bouton by special transporter molecules that are embedded in the presynaptic membrane, by absorption into nearby glial cells known as astrocytes (because they look like stars) or by [enzymatic deactivation](#), in which an enzyme cleaves the transmitter molecules so they become incapable of binding to the receptor. Finally, neurotransmitter may also be cleared from the synapse by diffusion: it simply floats away, putting it out of range of the receptors.

Neurotransmitters

As already mentioned, neurotransmitters are the chemicals that neurons release that allow them to communicate with one another. Up to this point, we have been discussing neurotransmitters in a generic manner, as if they came in only one flavor. Actually, they come in a variety of flavors, and many aspects of neural transmission are influenced by the type of neurotransmitter released into the synapse.

Our discussion focuses on two major classes of neurotransmitters found in the CNS. The first is the [amino acids](#), the smallest and most basic building blocks of proteins. Amino acids act as the main excitatory and inhibitory neurotransmitters in the brain. The other main class consists of neurotransmitters that are organized into “systems”; these neurotransmitters are produced by specific sets of neurons whose cell bodies are located subcortically and whose axons project diffusely throughout the cortex.

Before we turn our attention to the particulars of each of these classes, however, we must introduce the idea of neurotransmitter agonists and antagonists. [Agonists](#) are chemicals that mimic or facilitate the effect of a neurotransmitter on a target neuron,

whereas [antagonists](#) oppose or diminish the effect on a target neuron. Much has been learned about the functions associated with different neurotransmitters by examining the effects of agonists and antagonists.

Amino Acids: Glutamate and Gamma-Aminobutyric Acid (GABA)

The two main amino acids in the central nervous system that act as neurotransmitters are [glutamate](#), which has an excitatory effect, and [GABA](#) (gamma-aminobutyric acid), which has an inhibitory effect. You might wonder why there are both inhibitory and excitatory neurotransmitters. If only excitatory inputs existed, the system might careen out of control. Inhibitory inputs serve to dampen down, or modulate, the system. Think about a car, as an analogy. Imagine that the only way that one could control a car was via the gas pedal – by modulating “excitatory” input. You could indeed take your foot off the gas to slow the car down, but you could not do so very precisely or quickly. There is a need for the “inhibitory” input provided by the brake. Likewise, the nervous system must be able to both ramp up the activity of neurons and tone them down.

The main excitatory amino acid neurotransmitter in the CNS is glutamate. This neurotransmitter is used at approximately 15–20% of synapses in the CNS. Overactivity of glutamate in the brain is thought to play a role in the development of epilepsy, a disease in which an abnormal lowering of a cell’s firing threshold causes it to misfire. Too much glutamate can produce [excitotoxicity](#), which is excessive activity of receptors that can literally excite neurons to death. These neurons get “fried” by too much stimulation. In fact, excitotoxicity appears to be an unfortunate consequence of a particular form of brain damage, known as [ischemia](#), in which neurons die due to a lack of oxygen, most typically after blockage of a blood vessel in the brain.

The main inhibitory amino acid neurotransmitter is gamma-aminobutyric acid (GABA). About 40% of receptors in the CNS are GABAergic; as you can see, the use of inhibitory input is rather common. The inhibitory control provided by GABA is thought to be important for “fine-tuning” the pattern of activation across the nervous

system. For example, GABA appears to be important in dampening oscillatory, reverberatory excitation between the thalamus and cortex that could lead to the seizure activity associated with epilepsy (Olsen et al., [1999](#)). GABA has also been linked to other disorders, such as anxiety, insomnia, and schizophrenia (Möhler, [2008](#)). Many substances that reduce the activity of the CNS bind to GABA receptors. One such group of substances is [barbiturates](#) that reduce seizure activity and induce sedation and sleep. Another group are the tranquilizing drugs called [benzodiazepines](#), such as diazepam (Valium) and chlordiazepoxide (Librium). These drugs are generally used to treat anxiety disorders, but can also be used as antiseizure medication and to promote sleep and muscle relaxation. Alcohol also produces its anxiolytic (i.e., anxiety-reducing) and sedative effects by affecting GABA receptors.

Neurotransmitter Systems

The other main class of neurotransmitters differs from amino acids in that its members are organized into systems. These neurotransmitters are produced by neurons whose cell bodies are located subcortically and in the brainstem, and whose axons project diffusely throughout the cortex. Each of these neurotransmitters is released by a different set of neurons that together form a neurotransmitter system: the cholinergic, serotonergic, noradrenergic, and dopaminergic systems. Because these systems project diffusely throughout the cortex, each one can affect a large variety of behaviors, some of which overlap. Nonetheless, each system has been found to have some degree of specificity in influencing behavior.

Cholinergic System

Acetylcholine (ACh) is the neurotransmitter used in the cholinergic system. The cell bodies of neurons of the cholinergic system are located mainly in the basal forebrain nucleus and project to almost all portions of the cortex in a very diffuse and nonspecific manner (see [Figure 1.19A](#)). There are also cell bodies in the septal nuclei that project to the hippocampus. Both these nuclei are located between the hypothalamus and

orbitofrontal cortex. Because ACh is released in almost every cortical area, it tends to have a very general effect on neuronal and mental functioning.

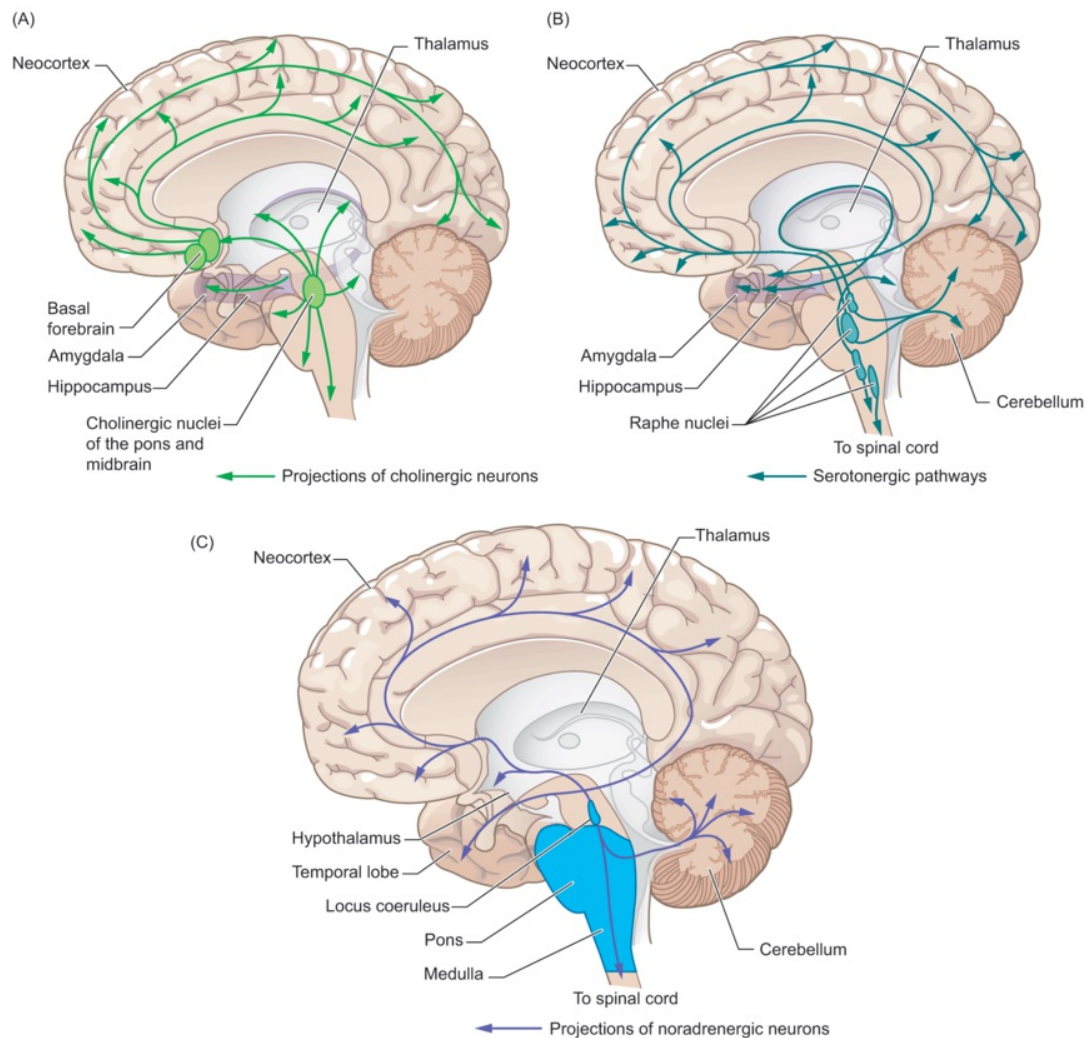


Figure 1.19 The cholinergic, serotonergic, and noradrenergic pathways in the brain.

(A) The cell bodies of cholinergic neurons can be found in the basal forebrain, pons, and midbrain. The axons of these cells project to the limbic system and neocortex and release acetylcholine in those locations. (B) The raphe nuclei in the brainstem contain the cell bodies of most serotonergic neurons. These neurons project to the cerebellum, limbic system, and cerebral cortex; they modulate mood, sleep, and appetite. (C) Neurons that release noradrenaline (norepinephrine) have their cell bodies located in the pons and medulla, most notably the locus coeruleus. These neurons project widely throughout the brain and spinal cord, allowing them to modulate overall states of arousal and vigilance.

The cholinergic system plays an important role in maintaining overall cortical excitability. ACh levels are decreased during anesthesia, when the brain is less active, and are increased by convulsants, which are drugs that produce seizure activity. ACh has also been linked to the production of rapid eye movement (REM) sleep, which is that portion of sleep when we dream and our minds are relatively active.

Given that ACh plays a role in overall cortical excitability, it may not surprise you that activity of the cholinergic system has been linked to paying attention (Sarter et al., [2005](#)). Cholinergic activity appears to be important for overall arousal or vigilance – the ability to stay alert, especially in boring or monotonous situations or over long periods of time. Nicotine, an acetylcholine agonist, can improve performance on tasks requiring sustained attention (Poorthuis et al., [2009](#)), which is one of the reasons people may find smoking cigarettes pleasurable.

ACh has also been linked to selective attention, which is the ability to attend to certain information while tuning out other information. ACh appears to sharpen the responses of cells to the features of stimuli that are most likely to make them fire, while suppressing responses to less prominent features of a stimulus (Sarter et al., [2005](#)). Another possible reason that people like to smoke is that nicotine can enhance the ability to filter irrelevant and annoying information from the smoker's awareness, allowing him or her to focus on new and important information (Kassel, [1997](#)).

Traditionally neuroscientists had also linked activity of the cholinergic system with memory processing because acetylcholine depletion is associated with Alzheimer's disease (Spillane et al., [1977](#)), which has devastating effects on memory as well as other functions, as we will learn in [Chapter 16](#). However, more recent evidence suggests that these effects on memory may be mediated by ACh's effect on attention (Klinkenberg and Blokland, [2010](#)). Clearly, if you are not paying attention to information when you first learn it, the information will be difficult to retrieve later on, because it was never well stored in memory. Therefore, some researchers suggest that ACh may affect both attentional and memory processes because it modulates an

operation required in both: selecting, or highlighting, certain types of information while discarding or ignoring other types (Bartus, [2000](#)).

Serotonergic System

[Serotonin](#), or 5-hydroxytryptamine (5-HT), is the neurotransmitter released by the serotonergic system. The cell bodies of the serotonergic system are found in several clusters located in the raphe nuclei of the midbrain, pons, and medulla (see [Figure 1.19B](#)). They project to hypothalamus, hippocampus, and amygdala, all of which are part of the limbic system, as well as to the striatum, cortex, cerebellum, and thalamus. Because of its diverse sites of projection, this system influences a large variety of behaviors, with the main ones being sleep, mood, sexual behavior, eating, and memory. Many of these behaviors are regulatory and help to meet an organism's basic needs.

One of the functions clearly associated with serotonergic function is sleep, and 5-HT levels can influence the level or stage of sleep, including REM sleep, which is associated with dreaming. Serotonin has also been linked to mood states, most notably depression, a state in which arousal levels are quite low (i.e., the person has no energy) and mood is continuously blue (see [Chapter 14](#)). Currently, some of the most popular drugs to treat depression are known as serotonin-specific reuptake inhibitors (SSRIs), because they do exactly that: they increase the amount of serotonin in the synaptic cleft by inhibiting its presynaptic uptake. You have probably heard of one of the best-known SSRIs, fluoxetine, known commercially as Prozac. While SSRIs can be very helpful in reducing depression, because the serotonin system is involved in a variety of regulatory functions, SSRIs have many other consequences as well such as interfering with sleep, reducing appetite, and impairing sexual performance.

With regard to cognitive function, serotonin has been linked most closely to memory, specifically the function of creating new memories for long-term storage (Schmitt et al., [2006](#)). For example, individuals given a diet lacking in tryptophan, a precursor to serotonin, show a specific deficit in forming new memories, whereas other cognitive functions are unaffected (Riedel et al., [1999](#)). Likewise, people with a history of using

the recreational drug “ecstasy” (3,4-methylenedioxy-methamphetamine), which is toxic to serotonergic neurons, tend to exhibit deficits in long-term memory (Zakzanis et al., [2007](#)).

Noradrenergic System

Noradrenaline (or norepinephrine) is the neurotransmitter emitted by cells of the noradrenergic system. The central noradrenergic system originates primarily in the locus coeruleus (see [Figure 1.19C](#)). Neurons in the locus coeruleus project to the thalamus, hypothalamus, and the cortex, most notably the prefrontal cortex.

The primary cognitive effect of increased activity in the noradrenergic system is to influence arousal and attention (Berridge, [2008](#)). Overall arousal is increased through action at receptors in the thalamus and cortex. Given this, it is not surprising that noradrenaline also plays a role in sleep. The receptors in the thalamus put the brain in a sleep mode, and noradrenergic cells also shut off during REM sleep. The only difference between waking and dreaming is noradrenaline!

Attention is influenced by noradrenergic receptors as well. Low doses of clonidine, which down-regulates the release of noradrenaline, degrade performance both when tasks require individuals to sustain attention and maintain vigilance (Coull et al., [1995](#)), when participants are “alerted” to an upcoming stimulus by a warning cue (Coull et al., [2001](#)). Given the association of noradrenaline with attentional functions, some researchers have suggested that the functioning of noradrenaline may be disrupted in attention-deficit/hyperactivity disorder (Biederman et al., [2006](#)) (see [Chapter 15](#)).

Functioning of the noradrenergic system has also been linked to both shorter-term and longer-term aspects of memory processing. One subset of noradrenergic receptors, the α receptors, have been linked to shorter-term memory, as noradrenergic agonists increase the ability of monkeys to retain memory over brief delays (Arnsten, [1998](#)). In contrast, activity of another set of receptors, the β -receptor subsystem, has been linked to long-term memory, especially memory that has an emotional component (Chamberlain et al., [2006](#)). For example, administering propranolol, which is a β -adrenergic

antagonist, reduces the heightened memory for emotionally charged information in both rats and humans (Cahill et al., [2000](#); Hurlleman et al., [2005](#); Reist et al., [2001](#)).

If you've noticed that some of the cognitive effects of the noradrenergic system overlap with those of the cholinergic system, especially with regard to arousal and attention, then you've been paying attention! At the end of this section we will discuss the reasons for these similarities, as well as interrelations among neurotransmitter subsystems.

Dopaminergic System

Dopamine is the main neurotransmitter used in the dopaminergic system. There are actually three dopaminergic subsystems: the nigrostriatal, mesolimbic, and mesocortical. These subsystems, shown in [Figure 1.20](#), are differentiated by the location of their cell bodies, the regions of the brain to which they project, and the effect they have on behavior. In a moment, we will examine each of them in more detail. But first, let's look at some characteristics common to all three subsystems.

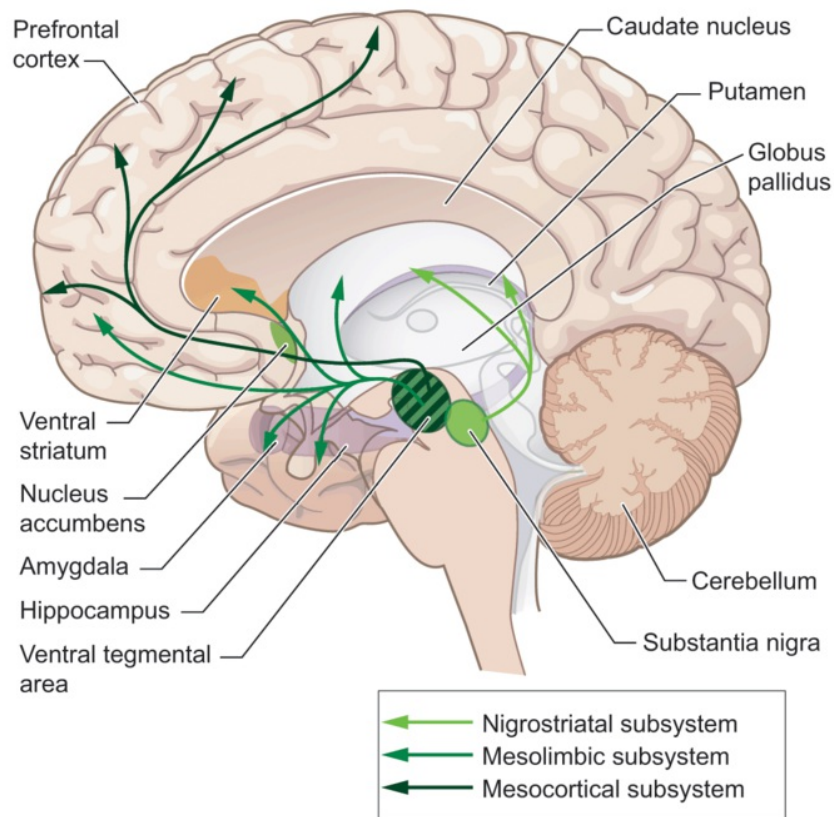


Figure 1.20 The three subsystems of dopaminergic pathways in the brain.

The nigrostriatal subsystem has dopaminergic neurons that originate in the substantia nigra and project to the striatum. This system contributes to motoric behaviors (light green arrows). The mesolimbic subsystem has dopaminergic neurons that originate in ventral tegmental area of the midbrain and project to limbic areas including the hippocampus, amygdala, nucleus accumbens, and ventral striatum (dark green arrows). This subsystem is involved in reward-related behavior. The mesocortical subsystem has dopaminergic neurons that originate in the ventral tegmental area of the midbrain and project to prefrontal cortex. This subsystem is involved in planning and working memory (black arrows).

Overall Characteristics

There are many different dopaminergic receptors, but they are divided into two main families: D₁-like and D₂-like. D₁-like receptors are located exclusively on postsynaptic sites, whereas D₂-like receptors are located both postsynaptically and presynaptically, where they serve as autoreceptors.

Many antipsychotic drugs work as D₂ antagonists. For example, chlorpromazine, one common antipsychotic drug, blocks D₂ dopamine receptors. These drugs often reduce the “florid” symptoms of schizophrenia, which are delusions (such as a belief that “The FBI is reading my thoughts”) and hallucinations (such as hearing voices that command a person to act in certain ways). However, they do not much alleviate the cognitive deficits and emotional withdrawal observed in patients with schizophrenia.

Rather, the severity of these latter deficits in schizophrenic individuals has been linked to the level of binding of D₁ receptors. For example, studies have found that there are more available D₁ receptors in people with schizophrenia than those without, especially in the frontal cortex (Abi-Dargham et al., [2012](#)). Therefore, at least some current research is focused on understanding how the relative balance of D₁ versus D₂ receptor activation may play a role in the symptoms observed in people with schizophrenia (Durstewitz and Seamans, [2008](#)).

Other receptors in the D₂ family also have specific effects on aspects of cognitive and emotional processing. One of these has been linked to a psychological trait known as “novelty seeking” (Benjamin et al., [1996](#); Munafò et al., [2008](#)), which is characterized by exploratory behavior, excitability, and impulsiveness. All of these characteristics are hallmarks of individuals who have trouble regulating their attentional control, so it is not surprising that genetic variability in the nature of these receptors may contribute to inherited aspects of attention-deficit/hyperactivity disorder (Nemoda et al., [2011](#)).

Subsystems

The first subsystem that we discuss is the [nigrostriatal system](#). The cell bodies of this system are located in the substantia nigra and project to the neostriatum (i.e., the caudate nucleus and putamen, also known as the basal ganglia; refer back to [Figure 1.12](#)). You may remember from earlier in the chapter that the caudate and putamen play a role in motor functioning, so it may not surprise you that this portion of the dopaminergic system is important in motor control. This subsystem does not control motor output as

much as it regulates the selection, initiation, and cessation of motor behaviors. As we will learn in [Chapter 4](#), it is the nigrostriatal dopaminergic subsystem that is affected by Parkinson's disease. In that disorder, the dopaminergic neurons in the substantia nigra die, depleting the caudate and putamen of dopaminergic input and leading to difficulties with motor control.

The second system, known as the [mesolimbic system](#), has its cell bodies in the ventral tegmental area, which is medial to the substantia nigra (see [Figure 1.20](#)). It projects to several parts of the limbic system, including the nucleus accumbens and ventral portions of the striatum, amygdala, and hippocampus, as well as prefrontal cortex. This system has been linked to reward-related behavior (Berridge and Kringelbach, [2015](#)). Dopamine levels in the nucleus accumbens increase in response to both natural reinforcers (such as food, drink, and sex) and drugs of abuse (such as amphetamine and cocaine). Additionally, in humans, activity in this region increases in response to more abstract rewards, such as money. We discuss the reward pathways in greater detail in [Chapter 12](#).

The cell bodies of the third dopaminergic subsystem, the [mesocortical system](#), are also located in the ventral tegmental area. The axons of these cells project to much of the cortex, especially motor and premotor cortex, as well as prefrontal cortex, where they influence a variety of mental functions. One of these functions is working memory, which allows us to keep information “on-line” for performance of tasks, planning, and strategy preparation for problem solving. Depletion of dopamine, but not of other neurotransmitters, produces a specific deficit in these cognitive functions of the dorsolateral prefrontal cortex, similar to that observed in animals that have had this area surgically removed. This effect has been linked specifically to D₁ receptors (Sawaguchi and Goldman-Rakic, [1991](#)).

As you can see, these neurotransmitter systems affect many different regions of the brain and have a variety of effects on cognitive and emotional processing. [Table 1.1](#) summarizes the main attributes of each.

| Neurotransmitter System | Transmitter | Site of Origin | Projection Sites | Main Receptor Types |
|-------------------------|--------------------------------|------------------------------|--------------------------|---|
| Cholinergic | Acetylcholine | Basal forebrain | Diffuse cortical regions | Muscarinic Nicotinic |
| Serotonergic | Serotonin | | | At least nine different receptors |
| Subsystems | | Dorsal raphe nucleus | Cortex Thalamus | |
| | | Medial raphe nucleus | Limbic system | |
| Noradrenergic | Noradrenaline (norepinephrine) | | | α_1 , α_2 , β_1 , β_2 |
| Subsystems | | Ventrolateral tegmental area | Hypothalamus | |
| | | Locus coeruleus | Thalamus Hypothalamus | |

Cortex

| | | | | | |
|-------------------------|----------|------------------------|-------------------|--------------------------------------|---|
| Dopaminergic | Dopamine | | | D ₁ family | 1 |
| | | | | (D ₁ & D ₅) | 1 |
| | | | | | 1 |
| | | | | D ₂ family | 4 |
| | | | | (D ₂ , D ₃ , & | 1 |
| | | | | D ₄) | 4 |
| | | | | | |
| | | | | | |
| Nigrostriatal subsystem | | Substantia nigra | Dorsal striatum | | 1 |
| Mesolimbic subsystem | | Ventral tegmental area | Limbic regions | | 1 |
| | | | Prefrontal cortex | | |
| | | | | | |
| Mesocortical subsystem | | Ventral tegmental area | Prefrontal cortex | | 1 |
| | | | | | 1 |

Interaction Between Neurotransmitter Systems

Although we have treated these neurotransmitter systems as if they were independent, they are actually highly interrelated. For example, both dopamine and noradrenaline are implicated in attention-deficit/hyperactivity disorder, they both have receptors in the prefrontal cortex, and they are both derived from tyrosine. Likewise, the serotonergic and cholinergic systems have been implicated in the formation of new long-term memories and sleep, and both project very diffusely to many regions of the brain. Both the cholinergic and the noradrenergic systems influence attention and memory. Given these areas of overlap, much current research is centered on how the various neurotransmitter systems interact (e.g., Olvera-Cortés et al., [2008](#)).

In Focus: Can Herbs Really Improve Your Memory, Attention, and Mood?

Balm is sovereign for the brain, strengthening the memory and powerfully chasing away the melancholy.

(John Evelyn, 1699)

Although we may think that the use of herbal supplements and therapies is a new and trendy approach to treating a variety of disorders, it is actually a time-honored tradition, as attested to by this quotation. Long used in Eastern medicine, and now increasingly in Europe and to a lesser degree in the United States, herbal supplements are being favored in some cases over standard pharmaceutical products. For example, in the United Kingdom, rosemary, lemon balm (a member of the mint family), and sage are used by herbalists and aromatherapists for memory problems. Probably one of the most commonly touted substances for reducing memory problems is ginkgo, which is derived from the leaf of the *Ginkgo biloba* tree, a plant native to China. It is widely prescribed in Europe, especially in France and Germany, for dementia. St. John's wort, an aromatic perennial that is native to Europe, is frequently used in Germany and other European countries to treat mild to moderate depression. Its effects have been known for a very long time, as evidenced by discussions of the herb by ancient Greek and Roman physicians such as Hippocrates and Galen. Kava, derived from a shrub native to Polynesia and the Pacific Islands and traditionally taken as a beverage mixed with water and coconut milk, is used to reduce anxiety and induce calm. Ginseng, derived from the root of a Chinese perennial, has been used to increase energy (Beaubrun and Gray, [2000](#); Kumar et al., [2012](#)). Saffron is thought to reduce depression (Modabbernia and Akhondzadeh, [2013](#)). Do these herbs have the claimed effect on thinking and mood, and, if so, how do they work?

There is much controversy surrounding the answer to this question. One source of controversy is the fact that in the United States such substances are not regulated by the Food and Drug Administration, so dosages and purity are not monitored. In at least one case, however, local use of a plant in Eastern Europe, the Caucasian Snowdrop (see [Box Figure 1](#)), for memory problems led to a new drug to treat Alzheimer's disease. Researchers there synthetically produced its active ingredient to create galantamine, now used in European countries and the United States, which has shown to be effective in slowing the decline associated with Alzheimer's disease (Kavanagh et al., [2011](#)).



Box Figure 1.1 A plant, the Caucasian Snowdrop, an extract from which is used to treat Alzheimer's disease.

The Alzheimer's drug, galantamine, is derived from an extract from this plant, which is a member of the daffodil family. Its mechanism of action is as an anti-cholinesterase inhibitor, and as such increases the amount of acetylcholine in the synaptic cleft by inhibiting its breakdown. This drug is an example of ethnobotany drug discovery, in which the local use of the plant in Eastern Europe led to investigations of its actions and then synthetic production of its active compound.

Credit: rsester/Getty Images.

And there is evidence of efficacy for at least two other herbs. For example, it was initially reported about 20 years ago in the Western scientific literature that ginkgo special extract EGb 761 slows the mental decline of individuals with

Alzheimer's disease (LeBars et al., [1997](#)). Since that time a variety of meta-analyses have documented its effectiveness at doses of about 240 mg in slowing the disease in people with mild to moderate Alzheimer's over the course of about a half a year as compared to a placebo (e.g., Tan et al., [2015](#); von Gunten et al., [2016](#)). In some cases, its effectiveness has been found to approximate the level achieved with standard pharmaceutical products, whose main action is to inhibit acetylcholinesterase (Wettstein, [2000](#); Mazza et al., [2006](#)).

However, it is not clear whether ginkgo aids cognitive performance in individuals who appear to be healthy; one large-scale study failed to find evidence that ginkgo enhances cognitive performance in healthy older adults (Solomon et al., [2002](#)). In addition, a longitudinal study found that ginkgo did not protect against the development of dementia in elderly people (DeKosky et al., [2008](#)). This study included more than 3,000 participants, age 75 or older, who were randomly assigned to receive either ginkgo or a placebo. Most of the participants had normal cognition at the beginning of the study, though some were characterized by mild cognitive impairment. The researchers followed these participants over about a six-year period, and found that participants in both the ginkgo and placebo groups were equally likely to develop dementia (see also Vellas et al., [2012](#)).

Another herb, St. John's wort, has been used to treat depression. A recent meta-analysis across 27 clinical trials, which together included close to 4,000 people, found evidence that St. John's wort is as effective as the current standard treatment, SSRIs, for mild-to-moderate depression. In addition, the discontinuation rate of use was lower, presumably due to less severe side effects (Ng et al., [2017](#)). Yet questions remain. First, these clinical trials were of relatively short duration, 4–12 weeks, so the long-term effects are unclear. Second, there is equivocal evidence as to whether St. John's wort is effective for

more severely depressed people, in part because there are fewer studies that have examined this issue (Apaydin et al., [2016](#)).

So how do these herbs affect the brain? It appears that many of them work on some of the neurotransmitter systems discussed in this chapter. Sage inhibits acetylcholinesterase (which breaks down acetylcholine) (Perry et al., [1996](#)) binds with muscarinic cholinergic receptors (Wake et al., [2000](#)), and is a GABA receptor antagonist (Kim et al., [2011](#)). Balm inhibits acetylcholinesterase as well as binding with nicotinic receptors (Perry et al., [1996](#)). Ginseng facilitates the release of acetylcholine (Benishin et al., [1991](#)) as well as the binding to muscarinic acetylcholine receptors (Kumar et al., [1997](#)). And saffron is thought to inhibit acetylcholinesterase (Geromicholas et al., [2012](#)). Thus, many herbs that are thought to help memory affect the cholinergic system, although any given herb may have numerous mechanisms of potential action.

St. John's wort inhibits the uptake of serotonin and noradrenaline, a mechanism of action similar to more commonly prescribed antidepressant drugs (Do Rego et al., [2007](#)). And ginkgo biloba has wide-ranging effects on neurotransmission (Montes et al., [2015](#)). On the other hand, some of these herbs have a very specific effect: for example, Indian ginseng affects only the cholinergic system, having no effect on GABAergic or glutaminergic receptors (Kumar et al., [1997](#)), whereas ginkgo appears to specifically affect the cholinergic system, rather than affecting all [monoamine](#) systems (Fowler et al., [2000](#)) (for reviews see Perry and Howes, [2011](#); Farahani et al., [2015](#)).

Herbs evolved to have such chemical properties, in part, to deter animals from eating them. For example, as we learned earlier, chemicals that affect the serotonergic system can also reduce appetite, mainly by inducing nausea. If eating a plant makes you feel sick, you are unlikely to ingest it again. However, in certain cases, as with St. John's wort, these adverse effects may be relatively mild, especially compared to its beneficial effects.

Interestingly, some herbs may affect the CNS through mechanisms other than

neural transmission. For example, ginkgo causes dilation of the blood vessels, which may allow more oxygen to reach the brain. Ginkgo also appears to help in dealing with molecules known as “free radicals” that can interfere with oxygen metabolism. In [Chapter 16](#), we discuss the degree to which defects in oxygen metabolism may underlie a large number of neurodegenerative disorders.

So, should you suggest to your older relatives that they start gobbling down scads of ginkgo, sage, St. John’s wort, and ginseng to ward off the mental declines that can accompany aging or to improve mood disorders? Probably not. As with any drug, dosage and interactions with other drugs, as well as effects on other bodily systems, are important. For example, one 36-year-old woman who ate 70 to 80 ginkgo nuts in an attempt to improve her health unfortunately had a very unexpected outcome: the herb induced seizures four hours later (Miwa et al., [2001](#)). St. John’s wort can affect blood pressure, intensify the effects of anesthetics, and increase the skin’s sensitivity to sunlight. It can also interact with a multiplicity of drugs because it interferes with a metabolic pathway in the liver that is used by many drugs to enter the body. Ginseng can interfere with the functioning of cells in the blood that aid in clotting. Nonetheless, it isn’t likely to hurt and might potentially be helpful to include saffron, sage, rosemary and other such herbs in your culinary repertoire.

Myelination

So far we have discussed the mechanics of how information is propagated from one neuron to another. However, we have not considered how information can be carried over long distances in the nervous system. The speed at which neurons propagate electrical signals down their axons depends on the degree to which the axon is insulated by a fatty sheath called [myelin](#). The larger the myelin sheath is, the greater the speed with which the electrical signal is propagated down the axon. The axons of some neurons have no myelin sheath. Unmyelinated neurons typically are small and do not

carry information over long distances; rather, they generally synapse on nearby neurons. In contrast, neurons whose axons project to distant places in the nervous system are typically myelinated, because myelination decreases the time needed to transport information from one neuron to the next.

To demonstrate the increase in speed afforded by myelin, let's consider a specific type of neuron in the brain known as a [pyramidal cell](#), which, among other things, is involved in controlling muscle movement. The axon of a pyramidal cell that controls movement of the right leg must extend from the brain to the bottom reaches of the spinal cord, a distance of more than 3 feet, or approximately 1 meter (m). Unmyelinated fibers convey information at the rate of only about 0.5 millimeter per millisecond (mm/ms). If the pyramidal neuron were unmyelinated, it would take approximately 2,000 ms (i.e., 2 seconds) to convey information from the brain to the base of the spinal cord ($2,000 \text{ ms} \times 0.5 \text{ mm/ms} = 1 \text{ m}$). Such a time delay would mean that people could not move or react very quickly. The myelination of pyramidal neurons allows information to be relayed at about 50 mm/ms, reducing the time between the generation of the signal in the brain to its arrival at the spinal cord more than a hundredfold, to about 200 ms.

The myelin sheath is not produced by the neuron, but rather by a particular class of glia. In the brain, these are known as [oligodendrocytes](#). A portion of the oligodendrocyte wraps itself around the axon much like a strip of carpet wrapped around a cardboard tube; such wrapping creates a discrete section of myelin ([Figure 1.21](#)). The more turns there are around the neuron, the greater the insulation and therefore the greater the conduction speed. Gaps between myelinated sections of an axon are known as [nodes of Ranvier](#). Because the electrical signal must jump across these nodes, they serve to keep the electrical signal constant in size rather than degrading as it travels down the axon.

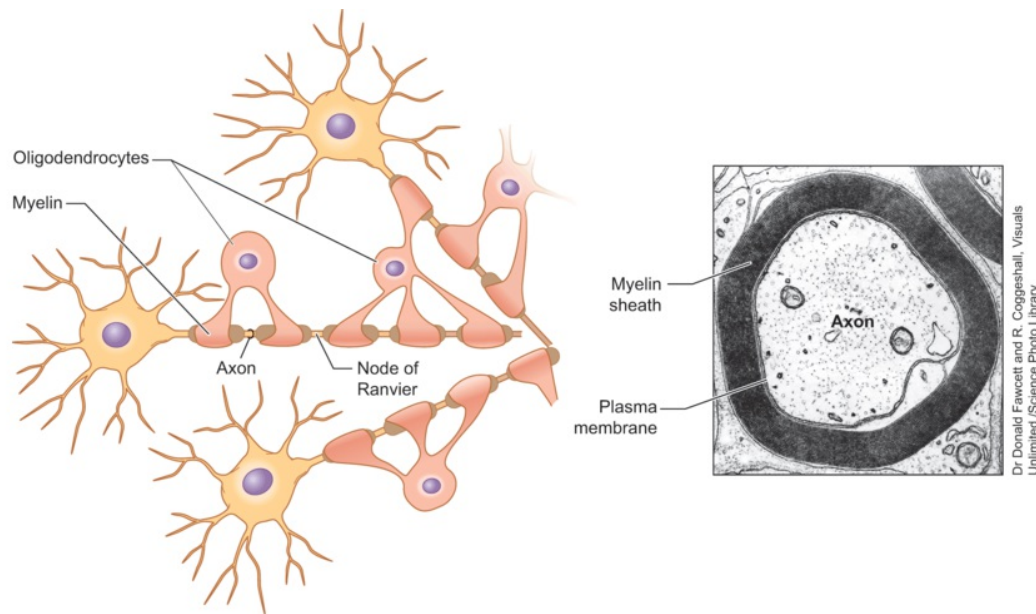


Figure 1.21 The structure of the myelin sheath around an axon.

Oligodendrocytes in the brain form a short section of the myelin sheath on each of a number of adjacent neurons by wrapping a paddle-like process around each axon. Gaps between sections of myelin, known as nodes of Ranvier, help the electrical signal to be propagated at a constant strength along the axon.

Because myelin is fatty, it is white. Areas of the brain through which myelinated fibers run are known as the white matter of the brain. Concentrations of unmyelinated cell bodies constitute the gray matter. When a group of cells sends their axons to the same place, the group of axons is known as a **fiber tract**, and because these axons usually traverse long distances, they tend to be myelinated. For example, the corpus callosum, which is the main fiber tract connecting the two halves (hemispheres) of the brain, is composed mainly of myelinated fibers, which allow a speedy transfer of information from a neuron in one hemisphere to a distant neuron in the other hemisphere. In fact, the cover of this textbook shows many of the long myelinated fiber tracts in the brain.

Later in this book, we discuss the myelination of neurons in the contexts of development and specific neurological disorders. As discussed in [Chapter 15](#), myelination of the brain follows a developmental course in which sensory and motor

regions myelinate early in life, but the connections between more distant regions involved in higher cortical processing do not become fully myelinated until as late as the mid-twenties (Simmonds et al., [2014](#)). The result is that regions of the brain become functionally more connected throughout adolescence (Stevens, [2016](#)). Some of the disease states we discuss later, such as multiple sclerosis (see [Chapter 16](#)), cause the myelin surrounding a neuron to be thinned in a patchy or haphazard manner. This process leads to a significant disruption in neural processing, affecting both motor function and cognitive function (DeLuca et al., [2015](#)). In people with multiple sclerosis, a greater degree of demyelination is associated with poorer scores on measures of quality of life (Mowry et al., [2009](#)).

A Closer Look at the Cerebral Cortex

Because the cortex plays a prominent role in many functions that we think of as uniquely human, we examine it in more detail. We begin by briefly discussing the anatomical characteristics of the cortex and a system of how cortical regions can be distinguished on the basis of the pattern of cellular organization, often referred to as cytoarchitectonics. Then, we examine regions of the cortex according to the functions that each serves.

Cytoarchitectonic Divisions

Although all regions of the cortex have five or six layers, or laminae, of cells, the relative thickness of each layer, as well as the size and the shape of cells within those layers, varies between brain regions. Neuroanatomists have identified areas of the cortex by grouping together those regions in which the laminar organization and nature of cells are similar. From these findings has emerged what is known as a [Brodmann map](#) (named after its creator), which divides the brain into distinct areas (shown on the inside back cover of your book in [Figures A and B](#)). Bear in mind that the boundaries on

the Brodmann map are neither absolute nor always distinct. Sometimes they reflect smoother transitions; therefore, the borders may be considered “fuzzy.”

Although the distinctions between regions in the Brodmann map are made entirely on the basis of anatomy, with no regard to function, in some cases regions with distinct cytoarchitectonic characteristics also have distinct functions. In other cases, the correlation between neuroanatomy and function is less clear. One of the main reasons to be familiar with the Brodmann map is that use of this system has become very popular with cognitive neuroscientists as a way to refer to particular regions of brain tissue. [Chapter 3](#) discusses the explosion of research utilizing brain imaging techniques that are designed to determine which regions of the brain are physiologically active during performance of a specific task. To convey the location of these regions to the reader, scientists often refer to the activated brain region by means of the number assigned to that region on the Brodmann map. For example, Broca’s area, a region of the left hemisphere that is important to speech output, is often referred to in Brodmann’s terminology as area 44 (abbreviated as BA 44, for Brodmann area 44). Alternatively, this same region could be called the frontal opercular region (see endpaper on the inside front cover, [Figure C](#): “Lateral view of the brain”).

Primary Sensory and Motor Cortices

The first region in the cortex to receive information about a particular sensory modality (e.g., visual information) is known as [primary sensory cortex](#). The [primary motor cortex](#) is the region of the cortex that is the final exit point for neurons responsible for fine motor control of the body’s muscles. The locations of the primary sensory areas and primary motor cortex are presented in [Figure 1.22](#).

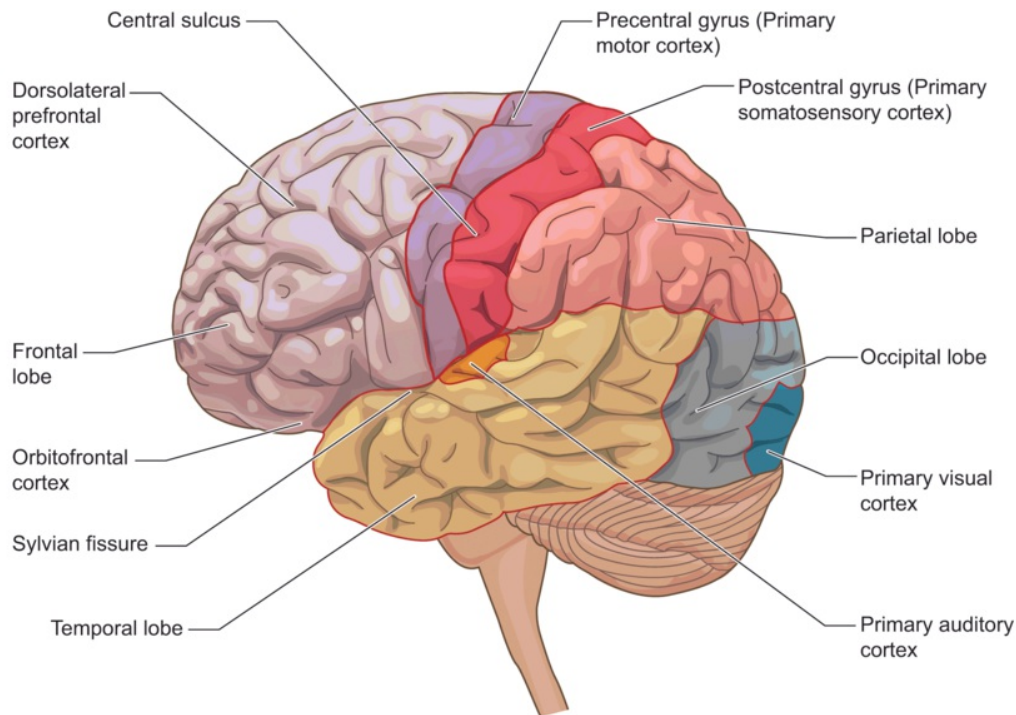


Figure 1.22 Primary sensory and motor cortices.

All the primary sensory areas are posterior to the central sulcus, whereas primary motor cortex lies anterior. The position of these primary sensory areas are shown in relation to the four major lobes of the brain: frontal, parietal, occipital, and temporal.

The primary sensory and motor areas share some general characteristics of organization that are worth noting now, although we leave discussion of the specifics of each system for [Chapter 5](#). First, all these brain areas are organized so that specific attributes of the physical world are “mapped” onto brain tissue. For example, in some alternative universe, we might have evolved so that the sensory receptors in the cochlea of the ear were organized to allow certain receptors to respond only to loud sounds and others only to soft sounds. However, in our world this is not the case. Rather, the [hair cells](#) in the cochlea of the ear are differentially sensitive to sounds of different frequencies (i.e., low tones versus high tones), which we perceive as tones of different pitch. Second, these maps are distorted relative to the physical world. They appear to reflect the density of receptors (or effectors) within a system. For example, we have a much higher density of receptors at the fovea, the focal point of our vision, than for more lateral locations. Likewise, much more of the primary visual cortex is devoted to

processing visual information from the central part of the visual world compared with the periphery. Third, the mapping of the world onto brain tissue occurs in an upside-down and backward manner for vision, touch, and motor control. For example, information from the upper right-hand portion of the body or world is processed by primary sensory or motor cortex in the ventral portion of the left hemisphere.

Motor Cortex

The primary motor cortex resides directly in front of the central fissure in a long, narrow band called the motor strip. It begins deep within the longitudinal fissure, rises up to the top of the brain, and then continues down to the Sylvian fissure. It falls mainly within Brodmann area 4. Look at [Figure 1.23A](#), which depicts the body regions that are controlled by each portion of the motor strip. This map is often referred to as the homunculus, meaning “little man.” As you look at [Figure 1.23A](#), note that a couple of features bear out the generalizations we just discussed. First, notice that the mapping of the body onto the brain is inverted with regard to both top and bottom and left and right. The left-right inversion occurs because the left motor strip controls the right side of the body and the right motor strip controls the left side of the body. The top-bottom inversion occurs because the area of the motor strip controlling the toes and feet is at the top end of the motor strip, actually within the longitudinal fissure, and the control of the face is most ventral on the lateral surface of the brain.

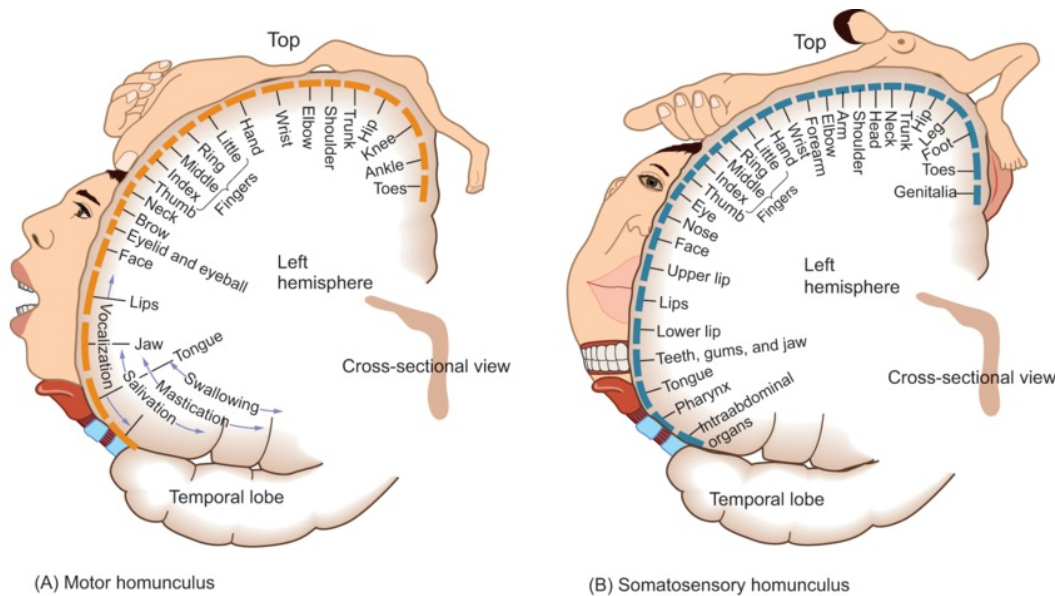


Figure 1.23 Maps of the motor homunculus and the somatosensory homunculus.

(A) Motor homunculus. Notice that the regions of the body for which we have fine motor sensitivity, such as the hand and fingers, have a large region of the motor cortex devoted to them. In contrast, large body parts for which we have relatively poor motor control, such as the leg, have a relatively small region of the cortex devoted to them. (B) Like the motor homunculus, the somatosensory homunculus is distorted. Regions for which we have fine tactile sensitivity, such as the hand and face, occupy larger regions of somatosensory cortex than those for which we have poorer tactile sensitivity, such as the trunk. Also notice that although the distortion is similar to that of the somatosensory homunculus, it is not identical.

Second, notice that the mapping is distorted, in that the area of brain tissue devoted to control of a particular body part is disproportionate to the size of that body part. Notice which regions of the body have large amounts of cortex devoted to their control despite their relatively small size: the face, the larynx, the vocal cords, and the hands. As you may surmise, the distortion of the map depends, in large part, on the degree to which we have fine motor control of a body part. The body parts for which we have a large degree of fine motor control, such as the face and the hand, have a disproportionately larger area of brain tissue devoted to their control than do areas of the body for which we have little fine motor control, such as the thigh.

Because the neurons in the motor cortex control the amount of force to be applied by muscles, damage to the primary motor cortex leads to muscle weakness on the contralateral side of the body. For example, damage to dorsal regions of the motor strip results in weakness of the bottom part of the body (recall the upside-down orientation of the homunculus), whereas damage to ventral regions of the motor strip often leads to weakness in face and arm muscles. As discussed in [Chapter 4](#), the body has multiple systems for muscle control. When massive destruction to the motor strip occurs along with damage to the basal ganglia (as often occurs after stroke), paralysis on the contralateral side of the body is observed and results in a deficit known as [hemiplegia](#).

Somatosensory Cortex

The primary somatosensory cortex is the portion of the cortex that receives information about tactile stimulation, [proprioception](#) (the perception of the position of body parts and their movements), and pressure and pain sensations from internal organs and muscles. It is located directly posterior to the central fissure in Brodmann areas 1, 2, and 3.

The skin contains various nerve endings, or receptors, that are sensitive to different aspects of tactile information, such as pain, pressure, vibration, and temperature. This information travels to the cortex along two main routes. Crude tactile information, along with information about pain and temperature, is sent to the cortex by neurons that synapse at dorsal regions of the spinal cord. From there information is carried to the thalamus and then to the cortex. Information about fine touch and proprioception enters the spinal column but does not synapse until the medulla, from which point it crosses over and is carried to the thalamus and subsequently onto the cortex.

Like the motor homunculus, the map of the body onto the primary somatosensory cortex is inverted left-to-right and top-to-bottom. The distortion of body parts in the somatosensory map is proportional to the density of touch receptors. In general, areas that have a high density of tactile receptors have large areas of the somatosensory strip devoted to receiving information from them, and areas of the body that have relatively

few tactile receptors have relatively small regions of brain tissue devoted to receiving information from them. The mapping of the body's sense of touch onto the somatosensory cortex is illustrated in [Figure 1.23B](#).

If you compare this map with that of the motor strip in [Figure 1.23A](#), you can see that the map of the somatosensory cortex looks similar but is not identical to that of the motor homunculus. The differences clearly arise because what is being mapped in the somatosensory strip is sensitivity of touch, not precision of motor control. Nevertheless, striking similarities are apparent. These similarities should not be surprising, because the parts of the body for which we have fine motor control, such as the hands, are the same areas for which we need a fine sense of touch. Agile manipulation of an object requires not only that we be able to move our hands and fingers, but also that our sense of touch be equally fine, so that we have tactile feedback on which to base our movements. If this relationship is not intuitively obvious, consider, for instance, how difficult it is to deftly manipulate something like your car keys in the winter when you are wearing a pair of gloves and your sense of touch is reduced.

Rather than obliterating all sense of touch, damage to the somatosensory strip impairs fine discriminations of touch on the side of the body contralateral to the damaged primary somatosensory cortex. So, for example, if you put a piece of cloth in the hand of an individual who sustained damage to the somatosensory strip, that person would know that something had been placed there but would have difficulty determining whether the cloth was velvet or burlap. Furthermore, if touched multiple times in quick succession, that person likely would have trouble determining the number of times she or he had been touched. Finally, if that individual were touched in two places near each other (e.g., two places on the back of the palm about 5 millimeters [mm] apart), he or she would have difficulty knowing that the touch had occurred in two separate places.

One interesting aspect of the somatosensory map of the body is that it appears to provide a means for understanding some phenomena associated with phantom limb pain, a symptom common after the loss of a limb. With phantom limb pain, the person usually perceives the missing limb to be in a particular position and may also perceive that it

moves. In addition to pain, the person may also perceive other sensations, such as itching. However, reorganization of the primary somatosensory region after limb loss can lead to some atypical feelings. For example, in the case of an individual who has lost a hand, touch on his face leads him to report that he feels the phantom hand. Although at first such a claim may seem odd, it really is not if you think about the organization of the somatosensory strip. By referring to [Figure 1.23B](#), you can see that the primary somatosensory region that receives tactile information from the hand is adjacent to the area that receives information from the face. In this individual, the reorganization of the somatosensory strip probably led neurons in regions previously devoted exclusively to receiving tactile information from the hand to interact with neurons that receive information from the face (Ramachandran et al., [1992](#)).

Visual Cortex

The primary visual cortex is the first region of the cortex that processes visual information. It is located in Brodmann area 17 in the occipital lobe ([Figure 1.24A](#)). We leave for [Chapter 5](#) a more detailed discussion of how information gets from the eye to the brain. For now, we will just highlight some basic attributes of this pathway that are important for understanding the mapping of the visual world onto the primary visual cortex.

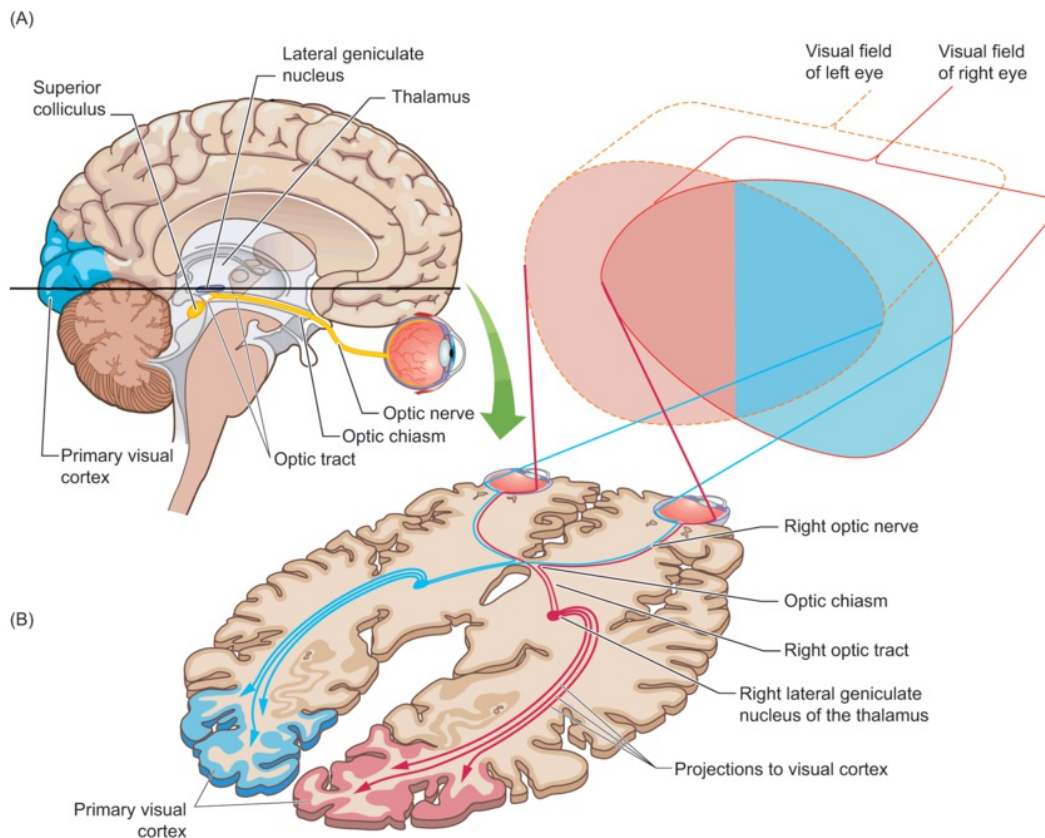


Figure 1.24 Pathway from the eye to the visual cortex.

(A) Midsagittal slice showing the location of the primary visual cortex of the left hemisphere. (B) Here the right visual field is depicted in blue and the left visual field in red. Information from each visual field reaches both eyes, but at the optic chiasm there is a partial crossing of information. The result is that all information from the left visual field projects to the right lateral geniculate nucleus of the thalamus and subsequently to the right primary visual cortex. Likewise, all information from the right visual field projects to the left lateral geniculate and subsequently to the left primary visual cortex.

To understand the organization of the visual system, take a look at [Figure 1.24B](#). When you look straight ahead, the information to the right of fixation, known as the [right visual field](#), projects to the left half of the retinas of both your eyes. Information to the left of fixation, known as the [left visual field](#), projects to the right half of the retinas of both your eyes. Except for information in the far periphery of the visual world, all visual information reaches both eyes. The far peripheral portion of the left side of the

visual world is detected only by the left eye (in part because the nose precludes the right eye from perceiving that part of the visual world); likewise, the far right side is detected only by the right eye. However, ultimately information from the right visual field is directed solely to the primary visual cortex of the left hemisphere, and information from the left visual field projects only to the primary visual cortex of the right hemisphere.

Destruction of the visual cortex results in an inability to perceive light–dark contrast. If the entire occipital cortex of only one hemisphere is damaged, no visual information can be detected in the contralateral visual field. This condition is known as an [homonymous hemianopsia](#). Sometimes just the dorsal or ventral portion of the occipital cortex is damaged, in which case just one quadrant of the visual world is lost, a disorder known as [quadrantopsia](#). In other cases, only small portions of the visual cortex are damaged, resulting in [scotomas](#), particular regions of the visual field in which light–dark contrast cannot be detected. To determine how well you understand the organization of the visual system, take a look at [Figure 1.25](#). Each picture shows a view of the visual world as it appears to a person with damage in a particular portion of the visual system. Try to determine the location of the lesion in the visual system for each situation shown.

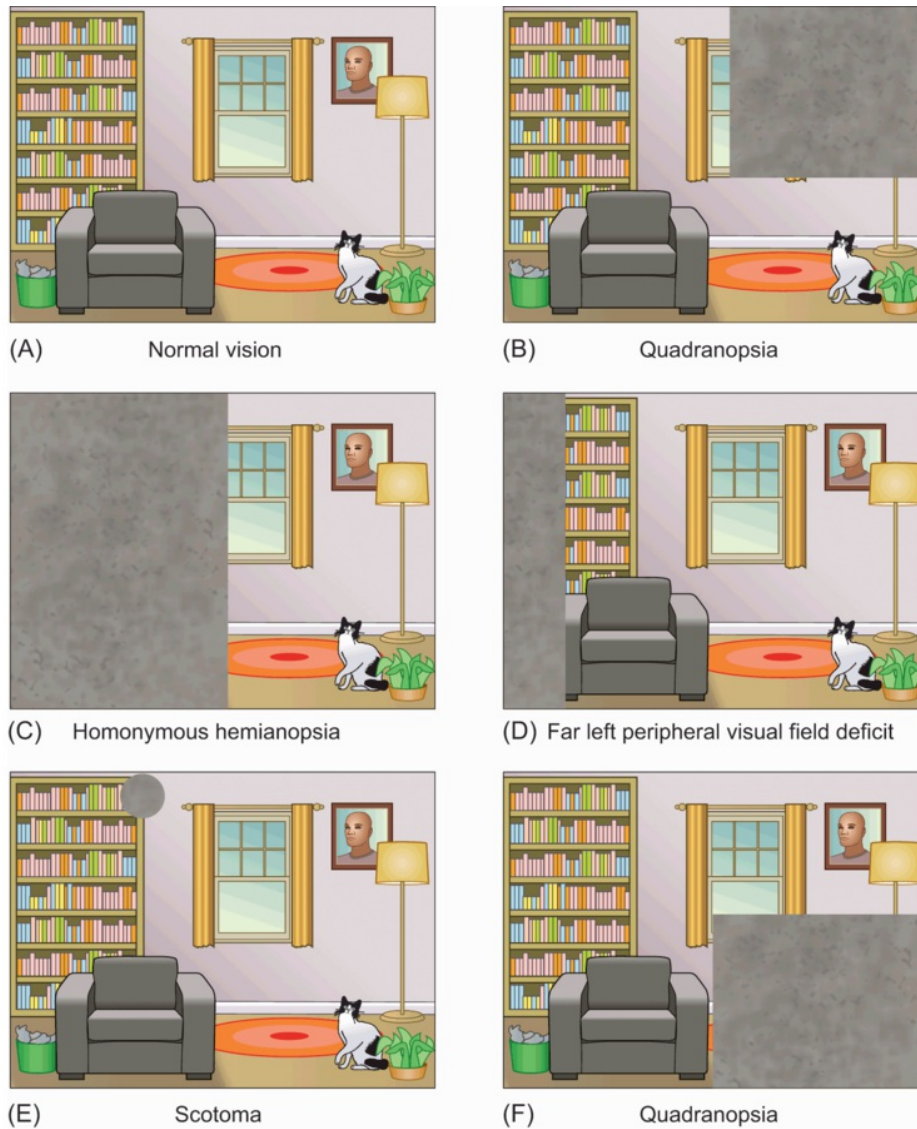


Figure 1.25 Visual field disorders.

(A) The visual world as it appears to an individual with an intact visual system. Where would the damage be located to create the views in (B), (C), (D), (E), and (F)? Answers: (B) Ventral regions of the left occipital lobe, (C) all regions of right occipital lobe, (D) damage to the left eye, (E) damage to a small portion of the ventral region of the right occipital lobe, (F) damage to the dorsal region of the left occipital lobe.

Auditory Cortex

The human auditory system is sensitive to sound, which is essentially pressure waves in the air. The physical energy in sound waves causes vibration of the eardrum and the

bones in the ear. These vibrations are transformed into pressure waves in a liquid in the cochlea, which contains hair cells that transduce pressure waves into a neural signal. [Chapter 5](#) discusses the route from the ear to the brain in more detail.

For now, it is important to know that unlike other sensory systems, in which information from one side of the body projects solely to the contralateral hemisphere, the auditory system is organized so that there are both ipsilateral and contralateral projections from the ear to the brain. Therefore, auditory information received at the right ear projects to both the left and right hemispheres. The primary auditory cortex of the human brain is located in the superior portion of the posterior temporal lobe in an area called [Heschl's gyrus](#), which is located in Brodmann area 41.

Like other primary sensory areas, the primary auditory cortex has a specific organization, described as [tonotopic](#), meaning that it is organized with regard to the frequency of a tone. In the auditory cortex, information from cells that all respond maximally to the same frequency converges on the same region of cortex. The mapping of the auditory cortex is such that the lowest tones are processed rostrally and laterally and tones of increasing frequency are processed more caudally and medially ([Figure 1.26](#)).

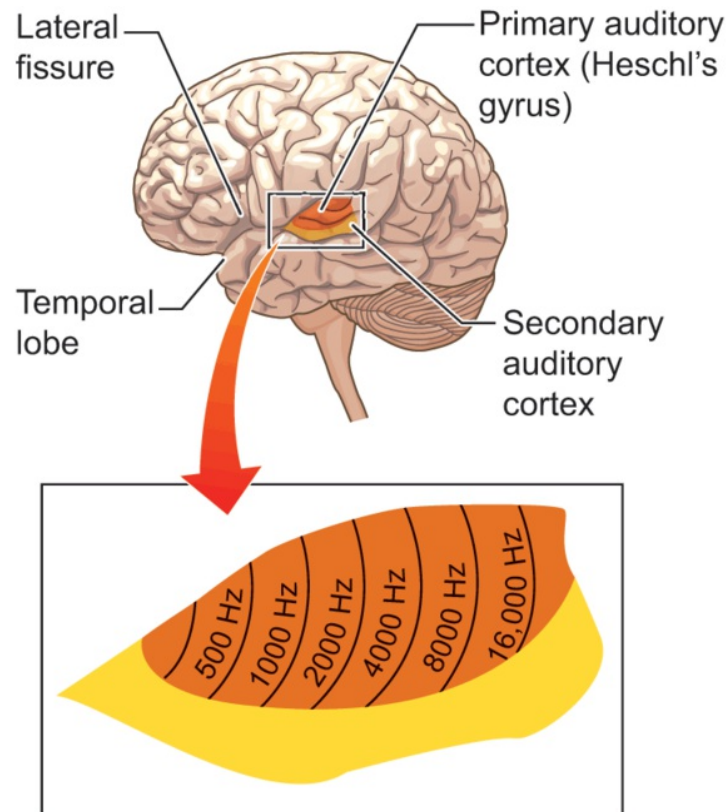


Figure 1.26 Location of primary auditory cortex and its organization.

The primary auditory cortex is located within the Sylvian (lateral) fissure. Its organization is tonotopic, with low-frequency tones processed more rostrally and also closer to the scalp, whereas high-frequency tones are processed more caudally and more deeply within the cortex.

Unilateral damage to the primary auditory cortex does not impair the ability to perceive all sound, because of the redundancy provided by both crossed and uncrossed connections in the auditory system. Damage to auditory cortex in one hemisphere alters the softest intensity that can be perceived – that is, the sound threshold. It becomes higher contralateral to the damaged hemisphere.

In addition, the ability to perceive the location of a sound becomes poorer for the contralateral side of space. If you have had a course in physiological psychology or perception, this finding should not be surprising. The mechanisms used to determine the location of a sound involve a comparison of the difference in the intensity and time at which auditory information arrives at each ear. Quite simply, if a sound is located

closer to your right ear than to your left, the sound will be louder at the right ear (and will arrive there sooner). Because unilateral damage to primary auditory cortex disrupts the ability to judge the loudness of sounds, you can see why people with such damage have difficulty localizing the source of a sound.

Olfactory and Gustatory Cortex

Our brains also have the ability to detect chemical substances in our environment, either those carried in the air, which are detected by the nose, or those contained in the food we eat, which are detected by the tongue. Our sense of smell comes from receptors in the nasal mucosa that send information about odors to the [olfactory bulb](#). Each of the two bulbs (one in each hemisphere) is a thin strand of neural tissue located directly below the frontal lobe ([Figure 1.27](#)). From the olfactory bulb, information is projected in one of two directions. One pathway, which probably mediates our emotional responses to smell, travels to various parts of the limbic system. Another projection goes via the medial dorsal thalamus to orbitofrontal regions, which can be considered the primary olfactory cortex.

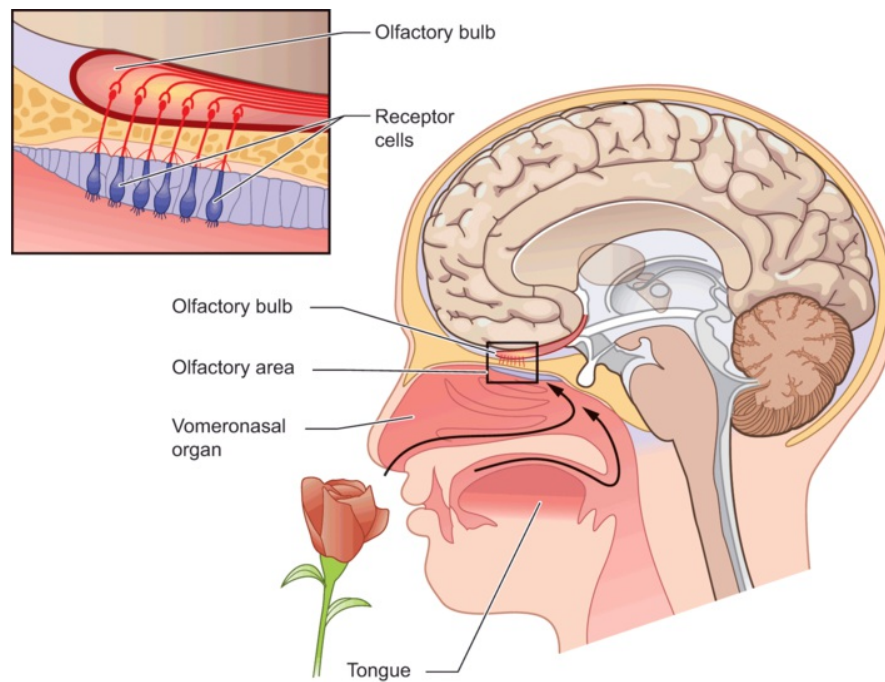


Figure 1.27 The olfactory system.

Human olfactory receptors reside in the nasal cavity where they receive airborne chemicals through the nostril. Their axons form the olfactory nerve, which sends information to the olfactory bulb.

Olfaction is unique in humans because it is the only sensory system in which information is solely conveyed ipsilaterally: Information received in the right nostril is sent to the right olfactory bulb, and information received in the left nostril is sent to the left olfactory bulb. Unlike the visual and auditory systems, in which we know that light–dark contrast and sound frequency, respectively, are the critical dimensions of the sensory world that the nervous system processes, the basic dimension by which smell is mapped onto the nervous system is unknown. What we do know, however, is that damage to primary olfactory cortex impairs odor discrimination in humans.

Our sense of taste comes from receptors in the tongue, known as taste buds. Like information from olfactory receptors, the information received by the taste buds and sent to the brain divides into two major branches, one going to portions of the limbic system and the other going to the primary sensory cortex ([Figure 1.28](#)). The primary sensory cortex for taste is located in the anterior portion of a region called the insula, which is

tucked inside the fold of the Sylvian (lateral) fissure. It probably should not surprise you that information from our sensory receptors of smell and taste go not only to the primary sensory cortex but also to portions of the limbic system that are involved in emotional processing. Think, for example, about how one refers to an unpleasant situation as “distasteful” or a dubious proposal or plan as “smelling rotten.”

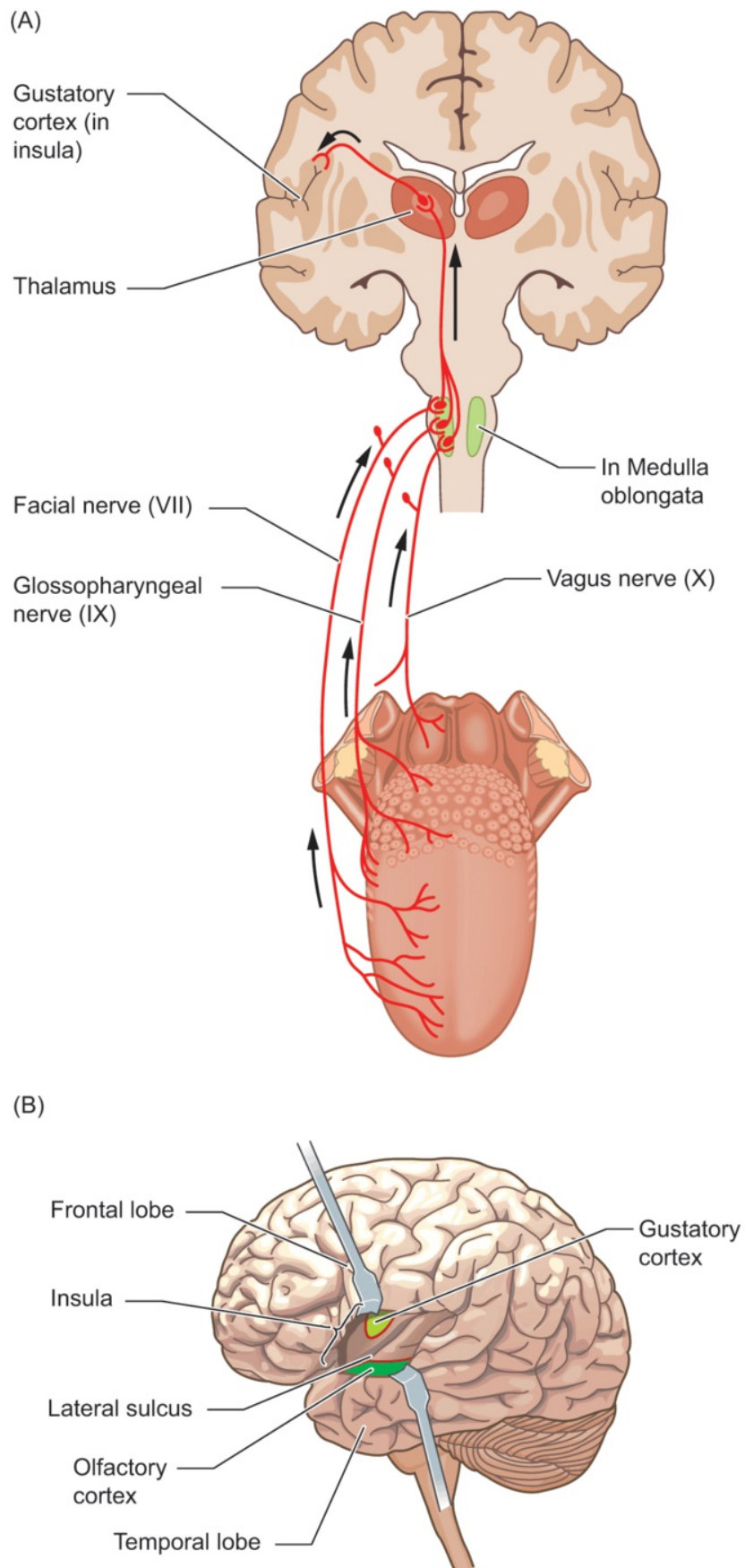


Figure 1.28 Relay of information about taste from the tongue to the brain.

Shown here are the major routes whereby information from the tongue reaches the brain. (A) Information from the tongue goes via the facial and glossopharyngeal nerves to the medulla and then to the cortex via the thalamus. The thalamus and cerebral cortex receive information from both the left and right sides of the tongue. (B) Location of that portion of the insula that serves as the primary cortex for taste.

At this point, we have discussed how sensory information is initially received and organized in the cortex. After processing by primary sensory regions, the information is relayed to secondary sensory cortex, which, like the primary sensory regions, processes information from only one sensory modality. However, secondary sensory cortex has a more specialized organization. For example, more than 30 regions of secondary visual cortex have been identified, each of which varies in its sensitivity to important visual attributes such as color, orientation, and motion. However, primary and secondary sensory cortices account for only a small proportion of the overall mass of the cortex. Next, we present an overview of the type of processing performed by the remainder of the cortex.

Association Areas

An area of the brain where information from multiple modalities is processed is known as an **association area**. As we shall see, these regions of the brain support the abilities that we tend to think of as distinctly human, such as language, compassion, and foresight. Because the occipital lobe is mainly involved in processing visual information, it does not serve as large an associative function as the other three major lobes of the brain. We now turn to a brief overview of the multiplicity of functions performed by each of these three lobes: the frontal, the parietal, and the temporal.

Frontal Lobe

Researchers and clinicians generally describe the frontal lobe as having three distinct regions: the primary motor region (previously discussed), the premotor region, and the

prefrontal region. Prefrontal regions are often further divided into dorsolateral, orbital, and medial regions ([Figure 1.29](#)). The distinction among these regions is based on major cytoarchitectonic subdivisions. In general, dorsolateral regions have been implicated in memory and executive function, orbital regions in emotional processing, and medial regions in judgment, decision making, and the detection of errors.

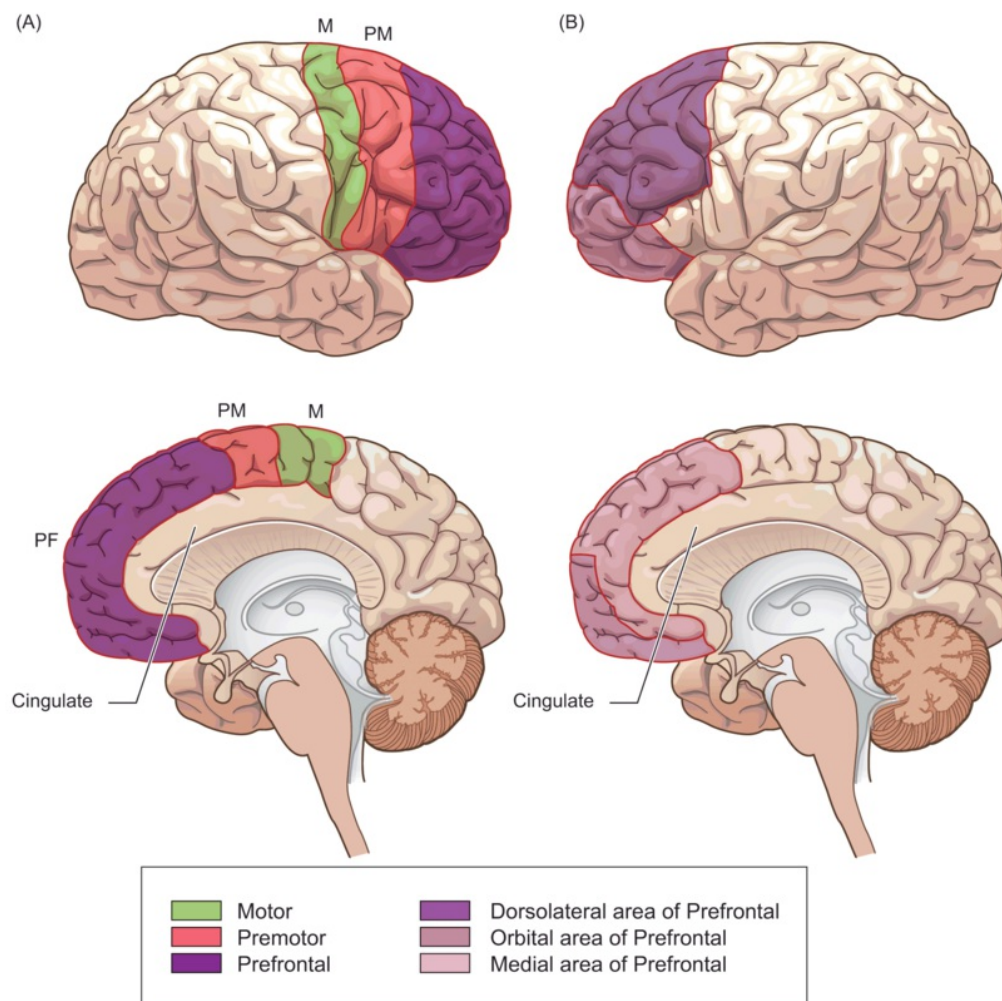


Figure 1.29 Divisions of the frontal lobe.

(A) The three major divisions of the frontal lobe; primary motor (M), premotor (PM), and prefrontal (PF) regions. (Top) Right hemisphere, lateral view. (Bottom) Right hemisphere, midsagittal view. (B) The prefrontal regions are further divided into dorsolateral, orbital, and medial areas. (Top) Left hemisphere, lateral view. (Bottom) Right hemisphere, midsagittal view.

Frontal regions are often considered the source of some of the most uniquely human abilities. A good generalization about the role of frontal regions is that they are associated with the planning, guidance, and evaluation of behavior. Just as the head of a corporation oversees its day-to-day operations and plans long-term goals for it, the frontal lobes are considered the “executive” of the brain. Not only are the frontal regions important for organizing behavior coherently, but research suggests that they may also allow us to extrapolate forward in time, enabling us to predict and consider the future consequences of our current behavior. We discuss these functions of the frontal lobe in more detail in [Chapter 11](#).

Frontal regions of the brain have been implicated in emotional functioning. Although we discuss the role of the frontal lobes in emotion in more detail in [Chapter 12](#), let’s briefly consider some important points. Commonly, the family and other loved ones of an individual who has sustained frontal lobe damage will comment that the individual just does not seem like himself or herself anymore. A formerly quiet and peaceful person may be described as argumentative and prone to outbursts, a previously conscientious and hardworking person may be characterized as irresponsible and lazy, and a previously kind and considerate person may now be called selfish and uncaring. In sum, people often say that the individual with frontal lobe damage has undergone a change in personality.

The frontal lobes have also been implicated in judgment and decision making. Individuals with frontal lobe damage often display poor judgment. These difficulties appear to result from both disordered cognitive processes and disordered emotional processes. For example, patients with frontal lobe injury are poor at systematically implementing strategies that would enable them to understand contingencies such as the set of conditions that lead to reward. Moreover, there is evidence that they have trouble interpreting those emotional or “gut feelings” that send us signals that “something just isn’t right” or integrating them with the facts about a situation (Bechara, [2004](#)). Some have suggested that medial regions of the frontal lobe are involved in monitoring

actions, allowing us to determine whether we have made an error. Such monitoring provides a mechanism for correcting behavior that does not lead to a reward or keeps one from reaching a goal (Taylor et al., [2007](#)). In fact, some have argued that this combination of emotional and rationale reasoning provided by the frontal regions plays a large role in moral reasoning (Moll and de Oliveira-Souza, [2007](#)).

As this short review illustrates, the frontal regions of the brain are involved in a vast array of behaviors. Rather than being important for specific domains of cognitive activity, such as language, spatial processing, or object recognition, frontal regions provide us with executive capabilities that are used across a vast number of domains and allow us to guide our behavior in a meaningful manner.

Parietal Lobe

The parietal lobe of the cortex plays a role in (1) integrating information from various sensory modalities, (2) integrating information from the sensory world with information stored in memory, and (3) integrating information about an individual's internal state with information from the external sensory world. Because this integrative function can occur in various ways, the deficits observed after parietal lobe damage are often diverse and difficult to conceptualize as all falling under the same rubric. However, if you keep in mind that the parietal lobe is critical for associating different forms of information, the array of functions performed by the parietal lobe will not seem all that disjointed.

In humans, the role of the parietal lobe in multi-modal integration is seen in many syndromes that occur after damage to this region, including alexia and agraphia. [Alexia](#) and [agraphia](#) are, respectively, the inability to read and the inability to write as a result of brain damage. [Chapter 8](#) discusses both these syndromes in more detail. The fact that alexia and agraphia are caused by parietal lobe damage makes sense if you consider what is involved in reading and writing. What we must do is take a pattern of letters (e.g., d-o-g) and associate it with meaning (e.g., a favorite household pet). Thus, reading

and writing, like other functions for which the parietal lobe is important, require different types of information to be linked.

Still another deficit observed after damage to parietal regions is [apraxia](#), which is the inability to link skilled motor movement to ideas or representations. Basic motor control is intact; the individual is not paralyzed. Although patients with apraxia can usually make skilled voluntary movements without difficulty, they cannot pantomime them. For example, an individual with apraxia could easily put a spoonful of sugar into her coffee cup, but when asked to pantomime the same gesture, she might use one finger to represent the spoon, rather than mimicking holding the spoon, twisting it to drop the sugar into the cup, and then rotating it to stir the sugar into the coffee. Apparently, patients with apraxia lack the capacity to program the motor sequences that allow the representation of an act, even though these persons have the capacity to perform the act itself. [Chapter 4](#) discusses apraxia more thoroughly.

Another ability affected by parietal lobe damage is spatial processing. Damage to parietal regions disrupts the ability to localize points in space, to know the angle of lines, and to understand spatial relations between items. Moreover, parietal regions of the brain also enable us to link spatial maps across different sensory modalities, and to integrate spatial information with motor movements. Consider the situation in which you hear but do not see a bird with a particularly melodic song. You want to know whether this bird is as pretty as it sounds. The parietal lobe will help translate the bird's probable spatial location, as deduced from auditory information, into coordinates in visual space. Moreover, it will aid in translating visual space into motor coordinates so you can move your eyes from their present location to the bird's probable location.

The importance of parietal regions in maintaining a map of space is seen most prominently in the syndrome called [hemi-neglect](#), or [hemi-inattention](#). In this syndrome, individuals ignore information on one side of space, usually the left, and act as if that side of the world does not exist. It is not that such individuals have sensory deficits that preclude them from processing information from the neglected region; rather, they do not direct attention to one half of the world, acting as if that region has

been erased from their spatial map of the world. More details about spatial processing and hemineglect are given in [Chapters 7](#) and [10](#).

As you can probably tell from this brief review, damage to the parietal regions can cause a heterogeneous array of syndromes. In general, however, they all are syndromes in which sensory information cannot be integrated either across modalities, with internal representations or memories, or with actions.

Temporal Lobe

Temporal regions of the brain are associated with four main functions: memory, visual item recognition, auditory processing, and emotion. The hippocampus in the temporal lobes was clearly linked to memory by the famous case of H.M. In early adulthood, he underwent bilateral removal of anterior portions of the temporal lobe for the relief of intractable epilepsy. Although the surgery was successful in reducing his seizures, he became unable to learn almost all types of new information, even though most of his memories from the years before the operation were intact. You will learn much more about the role of the temporal lobes regarding memory in [Chapter 9](#).

In addition to being important for the formation of new long-term memories, temporal regions of the brain play important roles in visual processing, contributing to visual item recognition. Electrical recordings from single cells in the inferior temporal lobes of monkeys have revealed that these cells respond only to highly specific visual stimuli. Unlike cells in the primary visual cortex, which respond to bars of light oriented at particular angles and moving in particular directions, the cells of the inferior temporal lobe respond to very specific shapes, such as a hand, a brush, or a face (Gross et al., [1972](#)). In fact, some of the cells may respond only to faces of particular people or certain features on a face, such as eyes (Perrett et al., [1987](#)). In people, damage to temporal regions can lead to deficits in recognizing common objects such as cars and chairs (Farah and Feinberg, [2000](#)), or in knowing that a given face belongs to a specific individual (De Renzi, [2000](#)). Thus, temporal regions appear to be important for

identification of visual items. [Chapter 6](#) discusses the role of the temporal lobe in visual item recognition in more detail.

This specialization of temporal regions for visual item processing and parietal regions for visual location processing seems to reflect a segregation of the processing of visual information in the mammalian brain into two streams or systems, one of which is important for processing the shape of items and the other of which is important for processing the location of items (Ungerleider and Mishkin, [1982](#)). One way to think about these two systems if you are a sports fan is to consider the contrast between a zone defense and a person-to-person defense. The parietal region of the brain treats items much the way a defender in a zone defense does. The job of these parietal regions is to process the location of items in space regardless of who they are. Thus, for parietal regions, localization of objects, not their identities, is important. In contrast, the temporal region of the brain treats items much the way a defender in a person-to-person defense does. These regions are sensitive to a specific person or object regardless of its location in space, just as a defender will stick to his or her target person regardless of where on the court or field that person may wander.

Because auditory processing areas are located in the temporal lobe, damage to this region can have consequences for the processing of auditory material. For example, damage in the temporal lobe can lead to an inability to recognize common sounds, such as a church bell, or to difficulties in the appreciation of certain aspects of music, such as melody.

Also associated with temporal damage are the syndromes of visual agnosia and auditory agnosia. An [agnosia](#) is a modality-specific deficit in recognizing sounds or objects that occurs in the absence of major deficits in basic sensory processing. What we mean by modality-specific is that the person cannot recognize an object in one sensory modality but can recognize it in other modalities. An individual with visual agnosia will be unable to identify an item as a rose merely by looking at it. However, if pricked by a thorn or catching the perfume of the flower, an agnosic individual will instantly recognize it. An important point about agnosia is that the deficit can be

attributed neither to the inability to perform basic sensory processing nor to a memory deficit. Persons with visual agnosia are not blind: they can distinguish light from dark, and can discriminate basic shapes (e.g., square from rectangle; Warrington and James, [1988](#)). For example, when looking at a rose, a person with visual agnosia can see that there is an object, describe its color, and maybe even crudely describe its shape, but cannot use this information to gather a visual impression of a rose. Furthermore, memory for an item is intact. Therefore, if asked which popular flower associated with romance has thorns or what flower makes up the garland placed around the neck of the horse that wins the Kentucky Derby, a person with agnosia could easily answer “rose.” Agnosias can also be observed in the auditory and tactile modalities as well. What is common to all these agnosias is that basic sensory processing in the affected modality is intact, as are memory processes. [Chapter 6](#) discusses agnosia in more detail.

Finally, temporal regions of the brain have also been implicated in the processing of emotional information, as discussed in more detail in [Chapter 12](#). Some structures in the temporal lobe are portions of the limbic system, which, as we learned earlier in this chapter, can act to integrate information from the sensory world with internal urges (e.g., urges for food, sex, and so forth). More recently, it has been suggested that portions of the temporal lobe are critically important for social and emotional processes, such as having empathy for others or for inferring what another person might be feeling or thinking (Saxe, [2006](#)).

White-Matter Tracts

Before we leave this broad overview of the organization of the nervous system, we also want to discuss how different regions of the brain are connected. One of the more important emerging themes coming out of brain research today is the fact that connectivity between brain regions plays an important role in supporting our thoughts and emotions. Throughout the text, we will point out research that addresses discusses these newer findings.

This connectivity is supported, in part, by white-matter tracts that shuttle information between distinct brain regions. Probably the most notable fiber tract in the human brain is the [corpus callosum](#), which connects regions of the left and right hemisphere. Although one typically views the corpus callosum in a sagittal section, where it appears as a single solid structure (see [Figure 1.30A](#)), it is important to realize that the corpus callosum is composed of millions of fibers in cross-section that vary in their degree of myelination (see [Figure 1.30B](#)), which then fan outward across the brain to connect homologous regions in each hemisphere (see [Figure 1.30 C](#)).

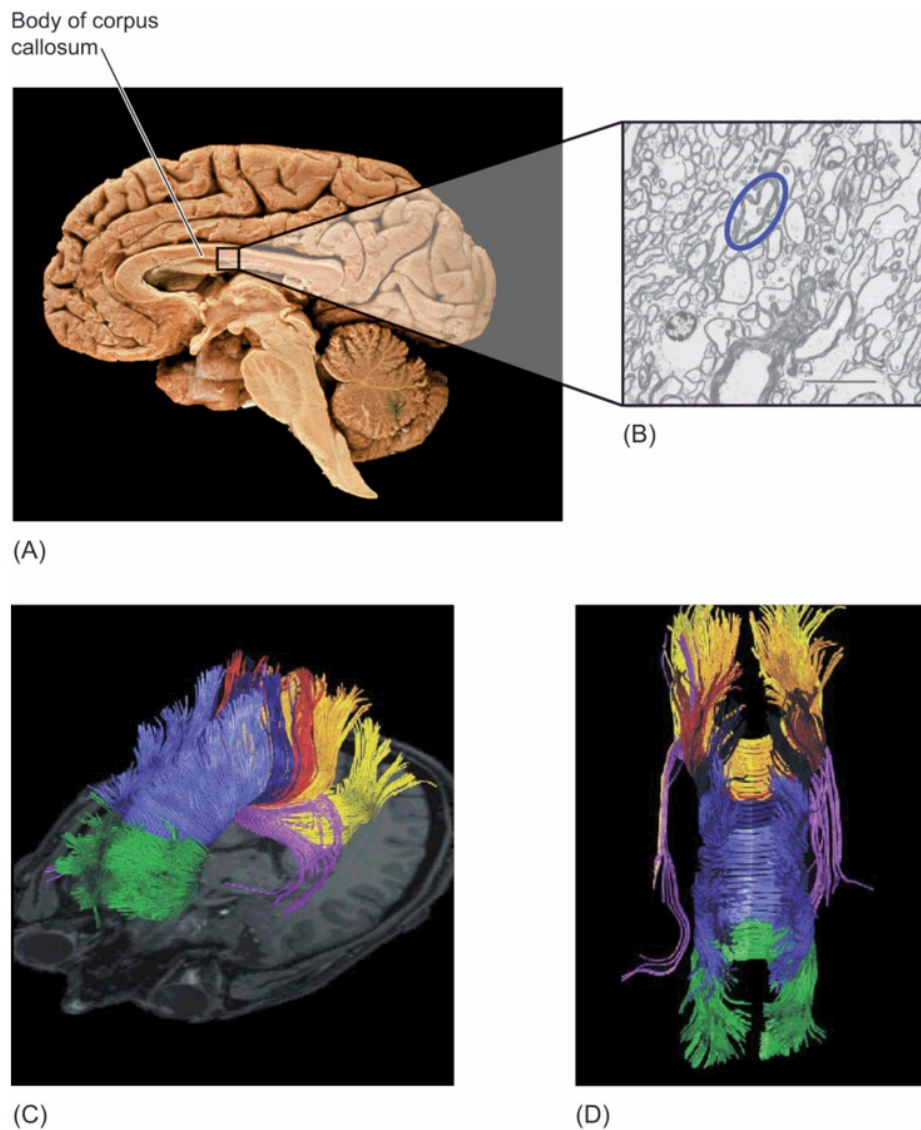


Figure 1.30 The corpus callosum, the major nerve fiber tract that connects the cerebral hemispheres.

(A) The corpus callosum as seen in gross anatomical cross-section. (B) The corpus callosum as seen in fine anatomical cross-section from a region similar to that noted by the box in (A). Notice the myriad of fibers that vary in their degree of myelination with one particularly well-myelinated fiber within the marked oval (from Aboitiz et al., [1992](#), figure 3). (C) and (D) Notice how the fibers in the corpus callosum fan out from the midline and bend upward (and downward) to create a set of rich connections between homologous regions of the hemispheres.

(from Hofer and Frahm, [2006](#))

[Figure 1.31](#) shows the major association fibers tracts of the human brain that connect regions within a hemisphere. The areas they connect are listed in [Table 1.2](#).

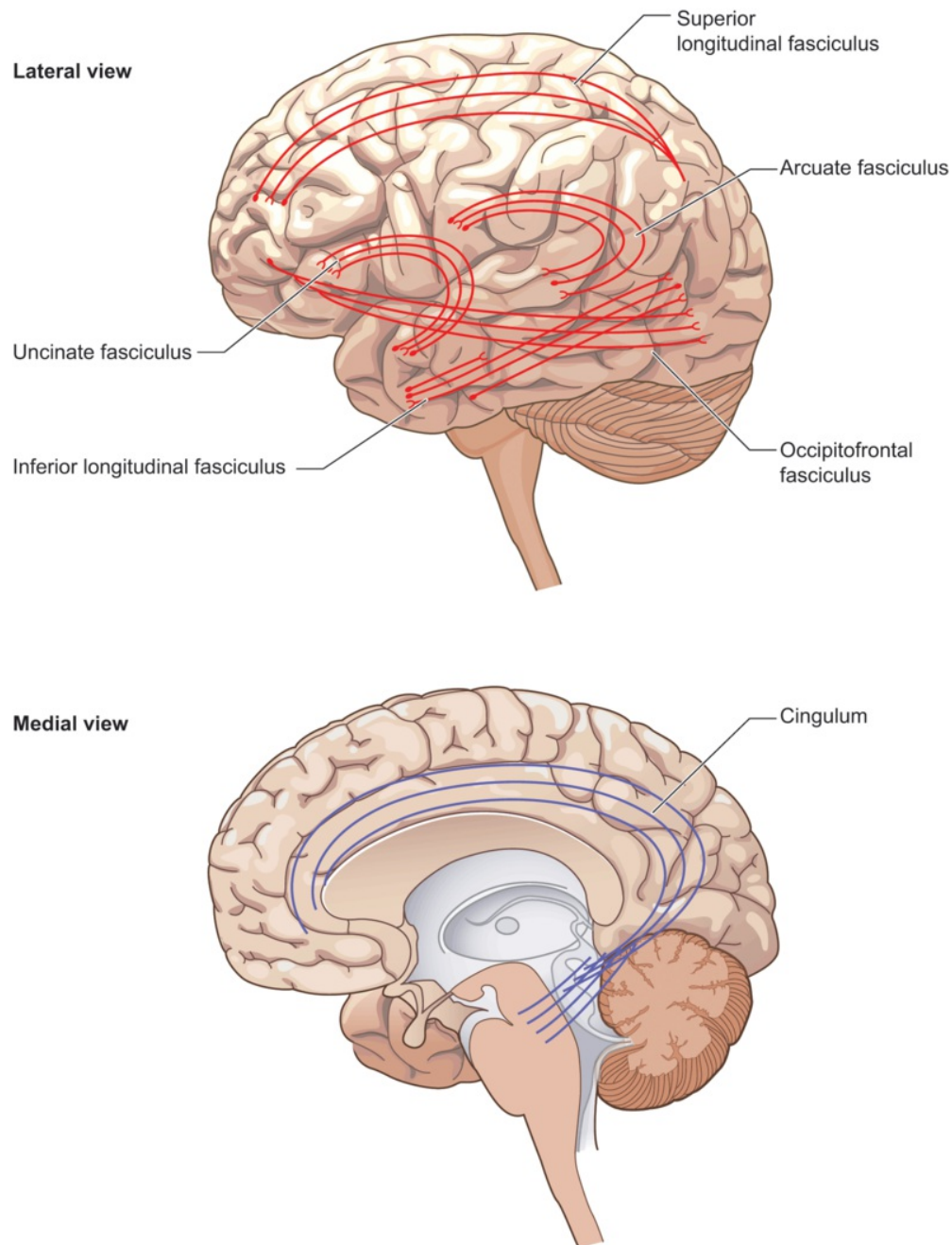


Figure 1.31 The major nerve fiber tracts that connect distant regions of the brain.

(A) Lateral view. (B) Medial view.

Table 1.2 The Main Nerve Fiber Tracts That Connect Regions Within a Cerebral Hemispheres

| Name | From | To |
|----------------------------------|--------------------|-------------------|
| Superior Longitudinal Fasciculus | Frontal | Parietal/Temporal |
| Occipitofrontal Fasciculus | Occipital | Frontal |
| Uncinate Fasciculus | Frontal | Anterior Temporal |
| Arcuate Fasciculus | Posterior Temporal | Frontal |
| Cingulum (located medially) | Frontal | Entorhinal Cortex |
| Inferior Longitudinal Fasciculus | Occipital | Temporal |
| Vertical Occipital Fasciculus | Occipital | Parietal |

To provide some perspective, a number of these fiber tracts link frontal regions to more posterior sections of the brain. Most of these course through more lateral regions. One of these is the superior longitudinal fasciculus, which links frontal regions to the parietal lobe. This fiber tract is important for attentional and executive control. Another tract is the occipitofrontal fasciculus that connects the occipital lobe to the frontal lobe. This links control structures in the frontal lobe with brain areas processing sensory information. Two tracts connect the frontal lobe to the temporal lobe, each of which links to a distinct portion of the temporal lobe. The uncinate fasciculus connects the frontal lobe to anterior portions of the temporal lobe. This tract is involved in emotional and language processing. The arcuate fasciculus connects posterior temporal regions to the frontal lobe and this tract aids in language processing. There is also a more medial frontoposterior tract, the cingulum, which wraps around the top of the corpus callosum

to connect frontal regions to medial temporal regions including the entorhinal cortex. This nerve fiber tract is important for memory processing.

Finally, two nerve fiber tracts connect posterior brain regions among themselves. The inferior longitudinal fasciculus connects occipital to temporal regions and is involved in object recognition and language processing. The vertical occipital fasciculus connects regions of the occipital lobe to the parietal cortex and it is involved in spatial processing and attention. As you can see, these fiber tracts efficiently shuttle information from far-reaching regions of the cortex to allow for a unified and integrated response.

In this chapter we have learned the terms that scientists use to talk about the nervous system and the brain, become familiar with the major subdivisions of the central nervous system, and gained a brief acquaintance with the role that each of these subdivisions plays. [Chapter 2](#) will provide a historical perspective on how we came to learn many of the facts presented in this chapter, so that you can better appreciate the plethora of methods available to cognitive scientists today, which are presented in [Chapter 3](#).

Summary

What Is Cognitive Neuroscience?

- Cognitive neuroscience comprises all investigations of mental functions that are linked to neural processes – ranging from investigations in animals to humans, and from experiments performed in the laboratory to computer simulations.
- Human neuropsychology is the specific study of linking brain function to mental processes in humans, usually inferred from examining the performance of individuals who have sustained brain damage.

Basic Building Blocks of the Nervous System

- Neurons are the cells that carry information by means of electrical and chemical

signals.

- Glia are support cells that serve as a conduit for transfer of nutrients to neurons and help repair damage to the nervous system.

Neuroanatomical Terms and Brain “Geography”

- Toward the front is known as anterior or rostral.
- Toward the back is known as posterior or caudal.
- Near the top of the head is known as superior or dorsal.
- Toward the bottom is known as inferior or ventral.
- Near the middle or midline of the body is known as medial.
- Toward the side of the head is known as lateral.

Major Subdivisions of the Central Nervous System

- The spinal cord is the main route for information coming into and leaving the nervous system.
- The medulla is important for controlling such life-sustaining functions as the beating of the heart and breathing, and for overall alertness and arousal.
- The cerebellum is important for skilled, coordinated motor movement and fluid cognition.
- The pons is the brain region at which information from many of the cranial nerves enters the nervous system.
- The midbrain is home to two important structures involved in orienting toward sensory stimuli: the inferior colliculus, which processes auditory information; and the superior colliculus, which processes visual information.

- The hypothalamus is important for motivational behavior, such as seeking food, seeking a sexual partner, and fleeing.
- The thalamus is a major relay center in the brain whereby information from the sensory world is reorganized on its way to the cortex and information from the cortex is reorganized on its way to the periphery.
- Major subcortical systems are the basal ganglia, which is involved in the control of movement; and the limbic system, traditionally thought to be important for emotion but now known to be involved in other functions as well, such as memory.
- The cerebral cortex is the main structure in the human brain; it is involved in processing sensory input, in controlling motor output, and in higher-order mental functions such as object recognition, spatial processing, and memory.

Electrochemical Signaling in the Nervous System

- Information is conveyed within a neuron via an electrical signal.
- An action potential, which is often referred to as the cell “firing,” consists of a change in the differential electrical charge across the cell membrane from -70 millivolts to $+40$ millivolts and back again.
- An action potential causes neurotransmitter to be released. The neurotransmitter chemical diffuses across the synaptic cleft and binds with specific receptors on the postsynaptic side of neighboring neurons.
- This chemical binding causes the production of postsynaptic potentials, which summate in time and space and can cause an action potential.
- The responsiveness of a neuron is limited by the time needed to “reset” before it can fire again.

- The effect of postsynaptic potentials is temporally limited by reuptake of the neurotransmitter by the presynaptic neuron, enzymatic deactivation of the neurotransmitter, binding at autoreceptors, uptake of the neurotransmitter by nearby glial cells, and diffusion away from the synaptic cleft.

Neurotransmitters

- Neurotransmitters are chemicals that are synthesized within the neuron and when released produce an action potential.
- Amino acids are the most common type of neurotransmitter in the CNS. The main excitatory amino acid in the CNS is glutamate, whereas the main inhibitory amino acid is gamma-aminobutyric acid (GABA).
- The other types of neurotransmitter are arranged into systems: acetylcholine is one type, and the monoamines – dopamine, norepinephrine, and serotonin – constitute the other type. The cell bodies for the neurons producing these neurotransmitters originate in subcortical and brainstem regions and project diffusely throughout the cortex.

Myelination

- Myelination is the process whereby oligodendrocytes wrap themselves around the neurons to provide an insulating fatty sheath around axons.
- Myelination reduces transmission time of information to and from disparate sites in the nervous system.
- Myelinated axons are referred to as white matter, in contrast to cell bodies, which are gray matter.

A Closer Look at the Cerebral Cortex

- Primary sensory cortex is the first place in the central nervous system at which information about a particular sensory modality is received from the peripheral receptors.
- Motor cortex is the final exit point for neurons controlling the fine motor functions of the body's muscles.
- Primary somatosensory cortex processes tactile information, including pain, pressure, texture, and the degree of pressure applied.
- Visual cortex processes the contrast between light and dark.
- Auditory cortex processes sound according to its frequency (pitch).
- The frontal lobe is the region of the brain involved in the planning, guidance, and evaluation of behavior.
- The parietal lobe is the region of the brain involved in multi-modal processing: integrating information across sensory modalities, memory, and an individual's internal state.
- The temporal lobe is the region of the brain involved in memory, visual item recognition, emotion, and auditory processing, including the processing of music.
- White-matter tracts connect distant regions of the brain. The corpus callosum connects homologous regions in the cerebral hemispheres, whereas a variety of fiber tracts connects anterior and posterior brain regions, as well as the major lobes of the brain.

Chapter 2

Historical Perspectives



[Ancient Times Until the 1800s](#)

[The Twentieth Century: Heyday of the Lesion Method](#)

[Single-Case Versus Group Studies](#)

[Inferences That Can Be Drawn From the Lesion Method](#)

[Limitations of the Lesion Method](#)

[The 1960s, 70s, and 80s](#)

[Studies With Nonhuman Animals](#)

[In Focus: Discovery of the “Homunculus”](#)

[Electrophysiological Methods](#)

[Disconnection Syndromes](#)

[Split-Brain Studies](#)

[Hemispheric Specialization: Left Brain, Right Brain](#)

[Testing the Isolated Hemispheres](#)

[Research With Individuals Who Have Lateralized Lesions](#)

[Research With Neurologically Intact Individuals](#)

[Theoretical Conceptions of Hemispheric Differences](#)

[In Focus: Left Out? Lateralization in Non-Right-Handers](#)

[Integration of Information Between the Hemispheres](#)

[The 1980s and 90s: The Advent of Brain Imaging](#)

[Anatomical Methods: Computerized Axial Tomography](#)

Functional Methods: Positron Emission Tomography
The Twenty-First Century: The Brain Imaging Revolution
Summary

As we will learn, cognitive neuroscience had very humble beginnings back in the time of the Romans, and was essentially dormant for close to two millennia thereafter. A surge of interest in anatomy, and the brain in particular, overtook scientists in Europe during the mid-1800s, pushing the field forward. This time period coincided not only with interest in mapping brain structure to function, but also with consideration and description of brain circuits that stand as part of the foundations of cognitive neuroscience today. The need to serve the veterans of the two World Wars, encompassing regions across the planet, led, among other factors, to a worldwide examination of the behavioral consequences of brain damage. Toward the end of the twentieth century and continuing on until today, there has been an explosion of methods that have allowed scientists for the first time to link brain structure and function to mental function in neurologically intact individuals. These methods have provided information at an exquisite level of anatomical and functional detail, and more recent methods drawn from computer science have allowed scientists to ask questions never before possible. As such, there has been and continues to be a stunning worldwide expansion of the field.

Ancient Times Until the 1800s

The seeds of the field of cognitive neuroscience were planted more than 2,000 years ago in the time of the Romans. Galen, a physician who ministered to the wounds of the gladiators, noticed that contestants sustaining injury to the arm, leg, or torso retained their powers of thought, whereas those who sustained injury to the head or the brain did not. From these observations, he inferred that the brain was linked to thought, and as such was the first to use patients with circumscribed brain damage to understand mental functions.

Galen's approach was a precursor of the logic we use today to determine which regions of the brain are important for a given mental function. If damage to a particular brain region results in an inability to perform a specific mental function, scientists usually assume that the function must have depended on that brain region. This approach is known as the [lesion method](#). During the history of neuropsychology and cognitive neuroscience, this method has proved immensely powerful in expanding knowledge about the neurological bases of thought and emotion. It has led us to conceptualize the brain as being composed of different subsystems, or modules, each supporting a different mental function. Although scientists have different ideas about exactly what constitutes a module (e.g., Fodor, [1985](#)), for our purposes it can be considered a portion of a processing system that is dedicated to a single function not performed elsewhere within that system (e.g., reading, verbal short-term memory, or face recognition). Furthermore, we now realize that these subsystems are located in specific regions of brain tissue, a concept called [localization of function](#).

This idea of localization of function first caught the attention of the scientific community in the 1860s, when Paul Broca, a French neurologist and anthropologist, provided evidence that a particular region of the brain is critical in language processing. Broca's discovery was sparked by an unusual patient whom he met on his rounds. The man could utter only the syllable "tan," yet it was clear that he could understand language because he could follow simple verbal commands. Because he did not exhibit paralysis of the vocal musculature or the vocal tract, Broca realized that the problem was specific to the brain's function of controlling speech output. When the man died soon after Broca met him, Broca autopsied his brain and noticed that a specific region of the left hemisphere was damaged (see [Figure 2.1](#)). Broca then accumulated brains from several other individuals who had the same type of language problem. In each case, the damage was restricted to the same brain region.

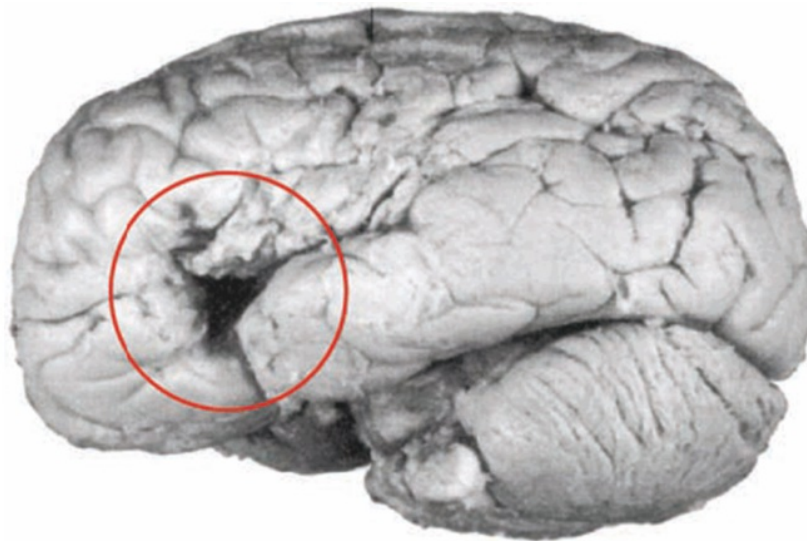


Figure 2.1 The brain of Broca's patient "Tan."

This patient was no longer able to say anything other than the syllable "tan"; his functioning, along with physical evidence from his autopsy, led Paul Broca to propose that a left-hemisphere region is crucial for speech.

(from Dronkers et al., [2007](#))

Subsequent evidence for localization of function was provided by other syndromes, such as Wernicke's aphasia, in which the ability to interpret spoken language is affected, but the ability to produce spoken language fluidly is intact. This behavioral syndrome was found to be associated with damage to a more posterior portion of the left hemisphere at the junction of the temporal and parietal lobes.

After these discoveries, a debate ensued in the early twentieth century as to whether functions are indeed localized or whether the brain works by [mass action](#), meaning that all pieces of brain contributed to all functions. One of the most notable supporters of the mass action viewpoint was the psychologist Karl Lashley, who did much of his work in this area in the 1920s and 1930s (Lashley, [1929](#)). He argued that the nature of cognitive deficits following brain damage hinged not on which region of the brain was destroyed but rather on the extent of the damage: The larger the amount of tissue destroyed, the greater were the decrements in performance. In contrast, researchers supporting the idea

of localization of function argued that the site of brain damage, not just the overall amount of destruction, predicted the nature and degree of the deficit observed.

Today, although we know that mental functions are localized in the brain, we also know that no brain region acts in isolation. Because of improved techniques for measuring lesions (or, in the case of animals, creating lesions), and because of more sophisticated methods for measuring behavior, researchers have realized that not all lesions have the same effect on behavior. Thus, behavioral differences must occur because of differences in brain structure. However, despite evidence of distinct subsystems in the brain, we must not forget that the brain is comprised of about 50 billion interconnected neurons. In fact, many newer approaches examine the characteristics of the brain as an integrated network and the influence of such characteristics on thinking and feeling. Consider by analogy a car. Although it is made of specific parts or systems such as an engine, a drive train, wheels, and suspension, all these parts are useless for travel unless they are interconnected in a specific manner so that the power from the engine can be transferred to the drive train to move the wheels.

Throughout this book, we will see that certain cognitive abilities, such as language, have been conceived traditionally as being organized in a modular fashion, with specific subcomponents such as those required for the comprehension of spoken language, the production of spoken language, reading, and writing each being performed by relatively distinct brain regions. In contrast, other cognitive functions, such as certain aspects of attention, are much more diffusely organized across many brain regions and require communication and connectivity across brain regions. Thus, we must remember that the brain relies both on localization of function and on distributed processing to carry out cognitive function in a seamless fashion.

The Twentieth Century: Heyday of the Lesion Method

The debt of cognitive neuroscience to the lesion method cannot be overstated. It allows a specific region of brain tissue to be directly linked to a specific aspect of mental processing. We can observe that when a particular region is damaged, a particular mental process is lost. Our ability to make such a link has been critically important to understanding many aspects of human cognition and emotion. While the advent of brain imaging has revolutionized our ability to examine the neurologically normal brain in exquisite anatomical and functional detail, those studies cannot reveal to us which brain regions critically support a given mental function. Only by observing the loss of function after the loss of brain tissue (or in more modern times during the electromagnetic disruption of brain activity) can we make inferences about cause and effect. In this manner, studies of patients with localized lesions continue to be invaluable to cognitive neuroscientists to this day.

Some of the darkest events of the twentieth century, those of World Wars I and II, had an unexpected effect. Physicians and other medical personnel were confronted with many veterans who had sustained head injuries during the war. This was especially the case after World War II, when survival rates increased and missile wounds to the head incurred during the war were relatively common. As a result, in hospital wards spanning from the United States to Spain, France, Italy, Germany, Japan, the Soviet Union, the United Kingdom, and beyond, there were young men with localized lesions who needed to be helped and treated. To do so required understanding the relationship between their injuries and the mental abilities they were likely to have lost, as well as those they retained.

The refinement of technology during the twentieth century, the X-ray, also helped to push the field of neuropsychology and cognitive neuroscience forward. As we just discussed, during the time of Broca and for the next 50–75 years, scientists and physicians could only make associations between brain and behavior when the person died and a postmortem examination allowed the site of damage to be determined unequivocally. As the damage had occurred years or decades prior, the brain might also

have potentially reorganized in response to the damage, thus somewhat obscuring the critical role of the damaged regions in behavior at the time of insult.

With the use of X-rays, physicians now had clearer information about which brain region was likely damaged, as they could determine which portion of the skull was missing due to entry of a bullet or another missile (see [Figure 2.2](#)). As such, patients could be grouped in some manner and associations with behavior noted. Generally, these divisions were rather gross in nature, for example, distinguishing between patients with anterior lesions from those with posterior lesions, or those with left hemisphere lesions from those with right hemisphere lesions. Note that the information provided by X-rays of the skull do not provide any hint of the extent or depth of the brain damage.

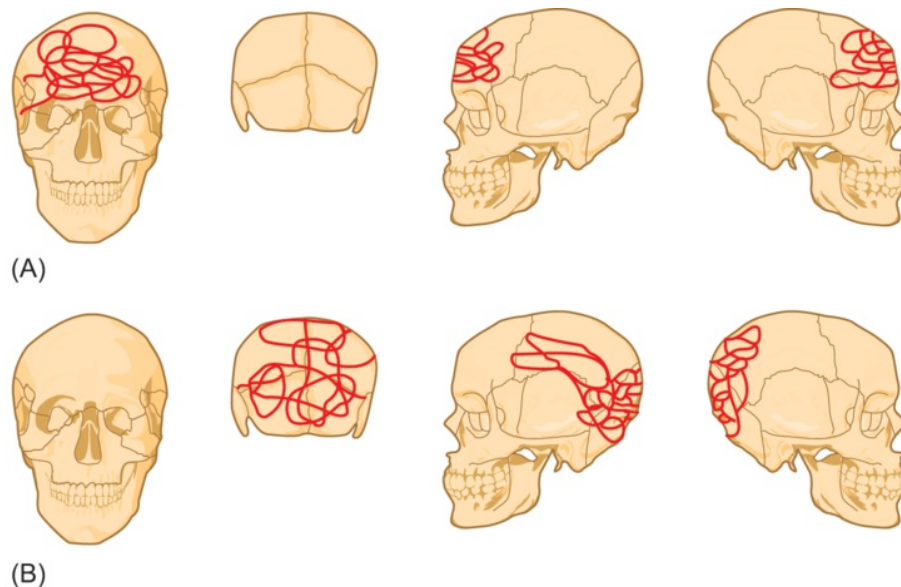


Figure 2.2 Composite diagrams of skull X-rays showing the entrance (and sometimes the exit) points of missiles that caused damage in two groups of 20 men.

X-rays were used in the days before brain imaging techniques to infer the extent and location of brain damage. Localization was not precise and allowed only gross differentiation such as that shown between (A) individuals with anterior lesions and (B) those with posterior lesions.

Another approach that pushed the field forward was work in which neurosurgeons excise portions of brain tissues, typically because they are the source of epileptiform (seizure) activity. The neuroanatomical extent of these “planned” lesions could be documented by the neurosurgeon performing the lesion. Furthermore, behavioral performance could be assessed before the surgery and then again afterward to determine which mental functions were specifically affected by the surgery.

A classic example of this approach began in the 1950s and continued for decades, spearheaded by Brenda Milner and colleagues at the Montreal Neurological Institute, who examined the role of the temporal lobe in memory. Their population consisted of patients who underwent unilateral surgical removal of portions of the temporal lobe as a treatment for epilepsy that could not be controlled by other means, such as drugs. Using this approach, Milner and colleagues demonstrated that removal (i.e., excision) of regions in and around the hippocampus within the temporal lobe is associated with difficulties in forming new long-term memories. Furthermore, by showing that damage to other brain regions, such as the frontal lobe, does not lead to such memory difficulties, the researchers concluded that the hippocampal region specifically supports the formation of new long-term memories (e.g., Milner, [1978](#)).

Single-Case Versus Group Studies

Scientists have leveraged the lesion method using both single-case and group studies of individuals with brain damage. In [single-case studies](#), a single individual with brain damage is studied intensively with a variety of neuropsychological tests. For example, the case of H.M., who received a bilateral temporal lobectomy (see [Chapter 9](#)), provided invaluable insights over 30 years into the role of the temporal lobe in memory. Because the memory loss he experienced after the surgery was so profound, no other individual has ever had this surgery, making him a unique but highly important case.

Nonetheless, relying on single-case studies for making inferences about brain-behavior relationships has its difficulties (see Zurif et al., [1989](#)). One problem is that we cannot be sure that the pattern observed for a single individual represents

people in general. For example, we know that left-handers, who constitute about 10% of the population, have a neural organization for cognitive function distinct from that of right-handers. If handedness, genetics, or some special environmental influence causes an individual's brain organization to be atypical, the pattern of disability after damage may be atypical as well.

In contrast, in [group studies](#), patients with brain damage who have similar characteristics (e.g., lesions in similar areas) are studied as a group. However, such studies are not without their difficulties as well (e.g., Caramazza and Badecker, [1989](#)). Group studies can be “messy” because the people within the group can be quite heterogeneous along a number of dimensions. Even if a researcher can assemble a group of patients in whom the lesion is in more or less the same location (e.g., the temporal lobe), the size, severity, and etiology of the lesions are likely to vary widely. In addition, individuals have had diverse life experiences both prior to and after brain damage. They may differ in their educational attainment, whether they grew up or live in rural versus city environments, their occupations and so forth. And their experience after damage may vary as well, depending on the type of rehabilitation they received, their attitudes toward therapy and recovery, and their social support networks.

To deal with this heterogeneity, scientists often use a [multiple-case-study approach](#). In this approach, findings for each individual within each group are provided, so that researchers can determine the variability across individuals as well as the degree to which the overall group average typifies the behavior of individuals within the group (see [Figure 2.3](#)). When a relationship between damage to a specific brain area and deficits is discerned despite variations in populations and differences in the nature of the damage, it is likely to be robust.

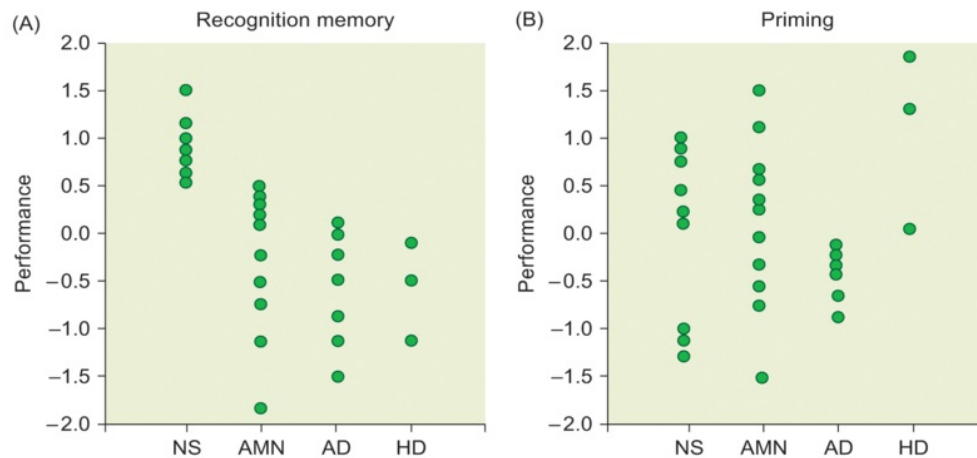


Figure 2.3 An example of the multiple-case-study approach.

To determine the extent of differences between patients with brain damage (AMN, patients with amnesia; AD, patients with Alzheimer's disease; HD, patients with Huntington's disease), and neurologically intact subjects (NS), the researcher treats each member of the group as a single-case study as well. (A) On a measure of recognition memory, every patient is performing at a level worse than that of the neurologically intact controls (0 indicates average performance, positive values represent above average performance, and negative values below average performance). (B) In contrast, on a measure of memory "priming" (i.e., facilitation of processing of material due to prior exposure), much more variability exists across the groups; the result is an overlap between the performance of the neurologically intact participants and that of the different patient populations. Whereas individuals with brain damage can clearly be characterized as having poorer recognition memory than controls, the same is not true for memory priming.

Multiple-case studies are also used to examine whether a relationship exists between a cognitive deficit and some other factor of interest, such as the amount of tissue destroyed. In the case of a previous example in this chapter, Milner and colleagues found that the degree of hippocampal damage is proportional to the degree of memory loss, providing additional evidence of this region's role in memory formation (e.g., Pigott and Milner, [1993](#)). A single-case study cannot address this question; it can

reveal only whether the hippocampal region is related to memory, not whether the degree of damage predicts the severity of the memory problem.

Inferences That Can Be Drawn From the Lesion Method

The major strength of the lesion method is that it allows us to determine cause and effect: damage to a given brain region leads to a specific and highly observable pattern of brain damage. The importance of the lesion method in expanding our knowledge in cognitive neuroscience cannot be underestimated. It has led to classic conceptualizations about the neural underpinnings of language, memory, and perception, to mention just a few areas (see Damasio and Damasio, [1989](#), for further discussion). Even today, when we have many new techniques for imaging the brain's structure and function, the lesion method remains an important tool for cognitive neuroscientists (Rorden and Karnath, [2004](#)).

Because the lesion method allows scientists to examine cause and effect, it also provides important insights into the architecture of the mind. Its power is increased by comparing patterns of what abilities are impaired and what abilities are unaffected. Such a comparison, especially when it exhibits a [double dissociation](#), provides a particularly powerful method for suggesting that two cognitive functions are independent of one another (e.g., Shallice, [1988](#); Teuber, [1955](#)). A double dissociation occurs when lesions have converse effects on two distinct cognitive functions: one brain lesion causes a disruption in Cognitive Function A but not Cognitive Function B, whereas a different lesion causes a disruption in Cognitive Function B but not Cognitive Function A. From such a pattern, we can infer that the functions can be independent, because the viability of one cognitive function does not depend on the viability of the other.

To make the concept of a double dissociation more concrete, let's consider a classic example, the dissociation between Broca's aphasia and Wernicke's aphasia. Both of these conditions involve disruptions in language processing (see [Chapter 8](#)). As a

starting point, we might hypothesize that all aspects of language processing rely on just one region of the brain. If this were the case, we would predict that if a person lost the ability to understand language, he or she would also lose the ability to speak. However, Broca's aphasia and Wernicke's aphasia illustrate that the ability to produce speech and the ability to comprehend speech are distinct. In Broca's aphasia, comprehension of spoken language is, for the most part, intact. However, people with this syndrome have great difficulty producing speech. People with Wernicke's aphasia display the opposite pattern. Such individuals cannot understand what is said to them but nonetheless fluently produce grammatically correct sentences (although, as we will learn later, these sentences are usually nonsensical). Considering these two conditions together, we see that disruptions in speech output are independent of whether a disruption in speech comprehension occurs, and vice versa. As such, we can infer that language is not organized as one monolithic block within the brain but has at least two subsystems: one related to comprehension and one related to production.

From the 1960s through the 1980s, researchers were especially keen to search for pairs or groups of patients who showed such double dissociations. Some of the patterns of dissociation are observed quite frequently, such as in the case of Broca's and Wernicke's aphasia. Nonetheless, other double dissociations rely on rare patients, either because the lesion location is highly atypical or because the specific type of behavioral deficit is so specific or restricted as to be hardly ever observed. In such cases, the purported dissociation of cognitive abilities needs to be interpreted more cautiously.

Limitations of the Lesion Method

Despite its power, the lesion method imposes a number of major limitations. Perhaps most importantly, a major limitation of the lesion method is that we cannot directly observe the function performed by the damaged portion of the brain. Rather, all that can be observed is how the rest of the brain performs without that particular area. From these observations we then infer the previous role of the damaged region. Although such

inferences are usually sound, they may have certain limitations and liabilities. First, only the regions of the brain critical to a given cognitive function can be identified, not the entire set of brain regions that may participate in that function. Second, a brain region's contribution to a particular cognitive function may be "silent," or masked, if the task can be performed in more than one manner. Individuals may remain competent at performing a given task by using an alternative strategy to that used before damage.

To appreciate the limitations of the lesion method in identifying all the brain regions that are involved in performing a task, think about putting on a play. If the person playing the main character is ill (and there is no understudy), the show cannot go on; therefore, we can identify that person as critical for the performance of the play. But if one of the stagehands or prop masters becomes ill, the curtain still goes up, even though clearly the missing individual contributed to the production. The show can continue because the chores of the remaining crew are likely to be shuffled to compensate for the absence of this individual. Similarly, if brain damage destroys a region that participates in but is not critical to the performance of a function, behavior can appear to be more or less intact, because other brain regions can act to take over or support that function.

Another limitation of the lesion method is that it may cause us to underestimate the role of a specific brain region in a given cognitive function. We may underestimate a region's contribution either because a person compensates by using a different strategy (that relies on intact areas) to perform the task, or because of reorganization of the brain tissue itself. For example, suppose that after damage to Region A of the brain, a person navigates around her or his world without much difficulty, leading us to assume that the functioning of Region A is unrelated to the cognitive skill of navigation. Yet, in actuality, Region A is important for navigation, playing a role in constructing the geographical relationship between objects or places (e.g., that the post office is to the east of the main shopping center). However, Region B of the brain provides the ability to navigate point to point by means of landmarks (e.g., the post office is six blocks past the church). It is possible to uncover the distinct roles of Regions A and B in navigation only if we carefully break down general cognitive skills into their components and test each

component individually, a task that sometimes can be difficult. Alternatively, a brain region may be critical for a function, but after damage the brain reorganizes so that the function is now performed by other regions that normally would not support the task. We discuss the issue of reorganization of function that can occur after brain damage in more detail in [Chapter 15](#).

The 1960s, 70s, and 80s

Studies With Nonhuman Animals

Until this point, we mainly have considered how scientists learned about the neural underpinnings of cognition by studying people. During this same time period, however, studies performed with nonhuman animals, most notably monkeys, also aided in expanding our knowledge. Although the brains of monkeys and humans are distinct, they appear to share several basic organizational principles, some of which are exhibited in all mammalian brains. Because monkeys can be trained to perform sophisticated cognitive tasks, classically many mental functions have been investigated with these animals, such as object recognition (e.g., Gross et al., [1972](#)), attention (Moran and Desimone, [1985](#)), and memory (Mishkin, [1982](#)), a tradition that continues today. Of course, some mental functions, such as language, are more difficult, if not impossible, to study in nonhuman species.

Studies using the lesion method with animals provide some advantages over those performed with people. They allow for better control over environmental conditions, the size and nature of lesions, and previous life experiences, than occurs in studies with humans. For example, animals can be raised in similar environments, they can be genetically similar (e.g., by using littermates), given the same type and size of lesion at the same age, provided with the same experiences before and after the lesion, and assessed behaviorally at the same age. In sum, their life experiences can be more carefully controlled. Thus, genetic and environmental characteristics of different groups of animals can be made as comparable as possible.

In addition to using the lesion method, much research with animals used (and continues to use) single-cell recordings. In these studies, an electrode is placed into the brain region of interest and the experimenter records the electrical output of the cell or cells that are contacted by the exposed electrode tip ([Figure 2.4](#)). After establishing a baseline firing rate for a given cell, researchers then determine what properties of a stimulus make the cell fire maximally above that baseline. Researchers use this technique to examine various issues. They may want to determine whether the cells are sensitive to input in only one sensory modality or are multi-modal in sensitivity; whether they respond to information from only specific places in the sensory world or from broad regions of space; and whether a cell's response is modified depending on whether or not the animal's attention is directed toward the stimulus.

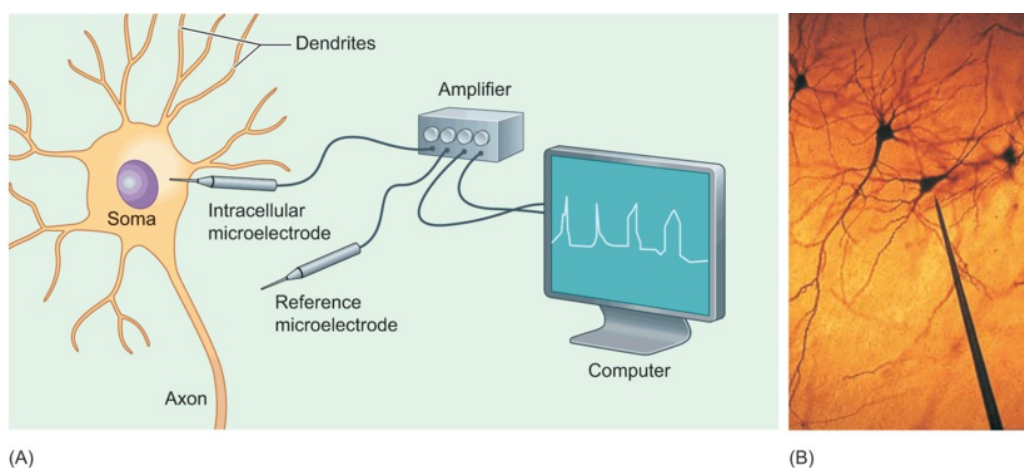


Figure 2.4 Single-cell recording.

(A) Shown on the left is a diagram of how information is recorded from single cells. The tip of an electrode, which is otherwise insulated, is placed in contact with the cell while the tip of another insulated electrode serves a reference. This information is fed into an amplifier and the activity is output on a computer monitor that shows the size of the electrical activity over time. (B) A photograph showing the tip of an electrode in contact with a cell body.

Courtesy of David Hunter Hubel, Department of Neurobiology, Harvard Medical School.

Studies involving single-cell recording techniques in animals have been enormously helpful in providing information about the organization of many brain regions. For example, such studies have demonstrated that cells in primary visual areas are responsive to basic orientation of bars of light, whereas cells in higher-order visual regions are responsive to much more elaborate forms (e.g., Desimone et al., [1984](#)); that frontal regions play a role in keeping information available in memory during a short delay period (e.g., Funahashi et al., [1991](#)); and that parietal areas are important for directing arm movements to particular regions of space (Georgopoulos et al., [1986](#)). Because studies such as these provide a basis for conceptualizing how particular regions of the human brain may be organized for certain cognitive functions, we discuss them throughout this text where appropriate.

It is important to note that today, just as with studies with humans, all research with animals must be approved by an ethical review board. The composition of these animal review boards is designed to provide a variety of perspectives, and generally includes at least one researcher, veterinarian, member of the community with no relationship to the institution, and a nonscientist. They review research protocols to ensure that the knowledge to be gained from the research justifies the use of animals, and that the animals are cared for and treated in the most humane way possible.

In humans, opportunities for such studies of single-cell recordings are limited. However, there are cases in which electrodes are implanted into the brain for about a week prior to surgery for the removal of epileptic tissue (see [Box Figure 2.1](#)). Such procedures allow precise localization of tissue that generates seizure activity and avoid the removal of useful, undamaged tissue. These procedures can also provide scientists with knowledge of the stimulus properties that make cells fire in a given brain region (e.g., Allison et al., [1994](#); Ojemann, [1983](#); Quian Quiroga et al., [2005](#)). Because opportunities to study the firing of single cells in humans are so limited, researchers often rely instead upon measurements of electrical activity of the whole brain via methods that we discuss briefly here and then in more detail in the [next chapter](#).

In Focus: Discovery of the “Homunculus”

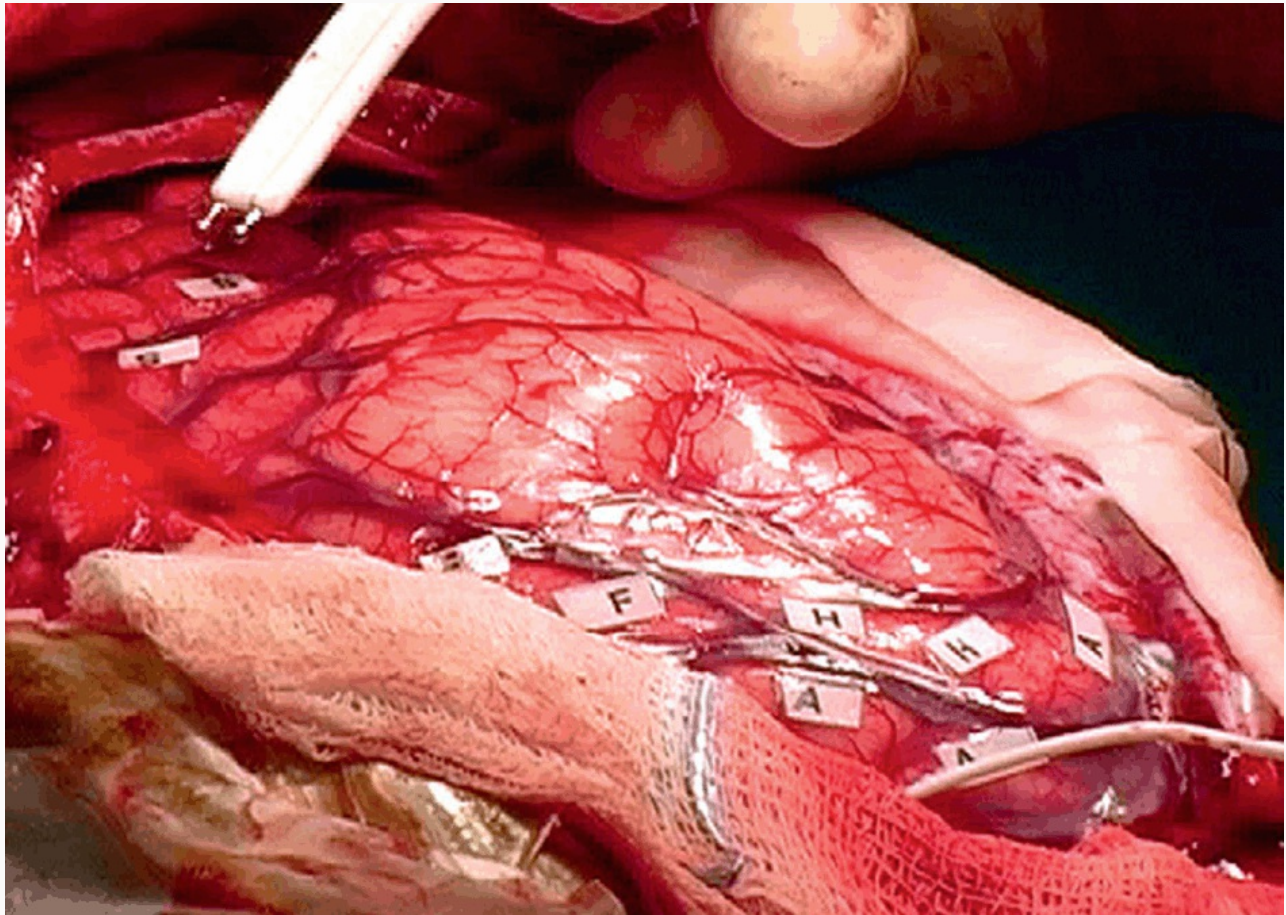
While the direct mapping of cells in the human brain is rare, as we discussed, it does occur especially in the context of the treatment of epilepsy. In fact, our knowledge about the organization of the motor cortex is derived in large part from such work. Although scientists knew from the late 1800s that the left motor strip controlled the right side of the body and vice versa, the precise nature of the homunculus was revealed only in the course of attempting to obtain a better understanding of epilepsy (Novelly, [1992](#)). Observations of a particular type of epileptic seizure known as Jacksonian seizure (named after the famous neurologist John Hughlings Jackson) revealed that the body was mapped onto the brain in an orderly fashion. During an epileptic seizure, neurons in the brain fire in an abnormal manner typified by great bursts, or volleys, of firing, often called spikes. In Jacksonian seizures, the tremors follow an orderly pattern, starting in one body part, such as the leg, and moving systematically to the trunk, then to the arms and face. Such a pattern indicates that the seizure begins in one part of the motor strip and proceeds along it in an orderly fashion.

In the mid-twentieth century, the creation of therapeutic interventions to reduce and control epilepsy dramatically revealed the degree of distortion of the brain map of the motor area. Working at the Montreal Neurological Institute, Wilder Penfield pioneered the use of surgical interventions to excise regions of brain tissue that cause epileptic activity (Penfield and Rasmussen, [1950](#)). Even today, when seizures originate from a specific brain region, often referred to as an epileptic focus, and cannot be controlled by drugs, physicians sometimes remove brain tissue at the focus. The rationale for this intervention is that continued seizure activity will recruit otherwise healthy neurons and cause them to become more prone to seizure activity. Although the neurosurgeon wants to remove the region of brain tissue that is misfiring, he or she must ensure that

neither the incisions required to reach the focus nor the removal of the misfiring tissue will have devastating effects. Therefore, the neurosurgeon needs to map out precisely which regions of the brain control which functions. This is especially true for the motor strip, because excision of portions of it can leave a person with severe muscle weakness on the contralateral side of the body. For these reasons, Penfield and his colleague, Henri Jasper, worked to create methods whereby electrical mappings of the brain could be performed prior to excisions (Penfield and Jasper, [1954](#)).

Let's move into the operating room to see how the mapping is performed. The patient is lying on the operating table, covered with surgical sheets that form a tent of sorts, with one open side around the patient's head. The patient's face protrudes from under one side of the tent, whereas the surgeon is situated on the other side at the opening of the tent. Procedure in this operating room is different from what you might expect: Instead of an unconscious patient on the operating table, this patient is alert and talking! Because the brain has no pain receptors, only local anesthetics are used as the surgeon removes a piece of skull to expose the brain underneath. After the brain is exposed, the surgeon places a tiny piece of metal, known as an electrode and connected to a very fine wire, on the brain. Then a sheet with a number is placed on the brain, adjacent to the electrode. Let's assume that the surgeon starts by placing the electrode directly in front of the central fissure at the most dorsal portion of the brain. Although the patient is lying perfectly still, as soon as the surgeon runs some current through the electrode, the patient's leg begins to twitch involuntarily! When the current is turned off, the twitching stops. The neurosurgeon then announces, "Leg movement at position 4" and moves the electrode more ventrally, leaving the marker in place. She or he now places another marker number on the brain and stimulates at the next spot. The patient's thigh begins to twitch. The neurosurgeon

continues in this fashion until the whole motor strip is identified (see [Box Figure 2.1](#)).



Box Figure 2.1 An example of mapping of motor areas in an individual by stimulation of brain areas.

Shown here is the stimulator that is positioned on different locations in the brain. The surgeon then observes what body part is affected by stimulation. Labels here show the area that resulted in movement of the arm (A), face (F), and hand (H).

(from Erickson and Cole, [2007](#), figure 1, page 540)

The need for such detailed, individualized mapping is obvious if you consider that each person's brain is as distinct as each person's face. Although neurosurgeons know that the motor strip lies in front of the central fissure, they do not know exactly where it is in any single brain. Consider by analogy the organization of the face. Just as we know that the eyes are always located above

the nose, so the neurosurgeon knows that the motor strip is in front of the central fissure. However, this landmark alone is not enough, just as knowing where a person's nose is located does not tell you exactly where his or her eyes are situated. Likewise, precise mapping is needed to determine the extent and range of the motor strip.

In addition to mapping the motor area, a neurosurgeon will also map the primary somatosensory cortex during surgery. In this case, the active cooperation of the patient is even more critical. Only a conscious patient can convey to the surgeon where the sensations, such as a tingle, a tickle, or an itch, are being felt as different regions of the somatosensory strip are stimulated. This mapping technique, originally designed to aid the neurosurgeon in therapeutic interventions for epilepsy, has provided extremely useful information about the organization of the primary motor and somatosensory areas, as well as language areas.

Electrophysiological Methods

Even though during the mid-twentieth century single-cell recordings were relatively rare in humans, scientists at this time were leveraging and creating new methods for recording the electrical signals that the brain is generating at the scalp. For quite some time, [electroencephalography \(EEG\)](#) had been used to record brain activity via about 20 or so metal electrodes positioned on the scalp ([Figure 2.5](#)) and then amplified. In EEG, each electrode (sometimes called a lead) acts as its own recording site or channel. This method was invented in 1924 when Hans Berger first recorded the brain's electrical signals from individuals with skull defects (for a history of early EEG research see Stone and Hughes, [2013](#)).

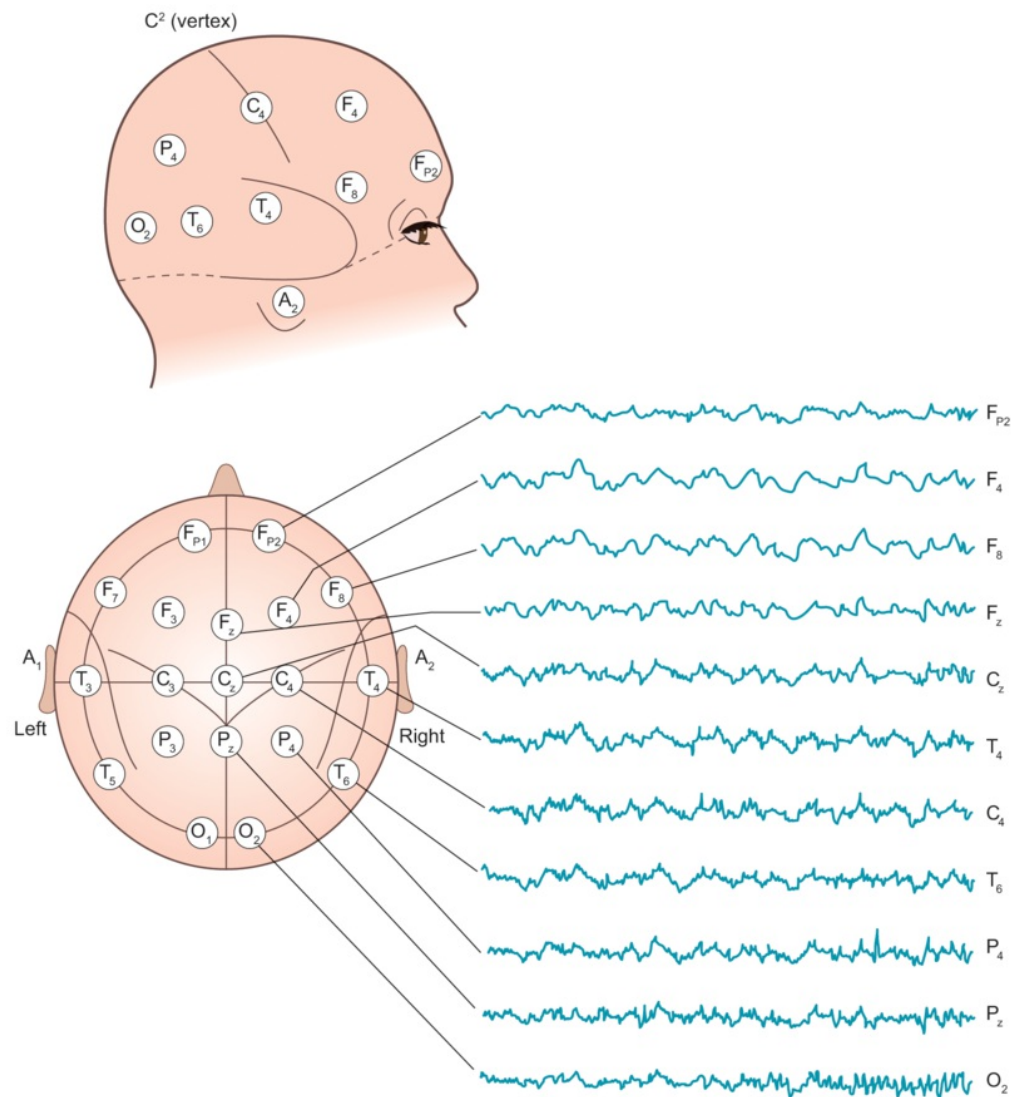


Figure 2.5 Standard placement of electrodes during electroencephalography recording for a standard 20-lead system.

Electrodes over the left hemisphere are labeled with odd numbers, those over the right hemisphere are labeled with even numbers, and those on the midline are labeled with a z. The uppercase letter is an abbreviation for the location of the electrode: A, auricle; C, central; F, frontal; Fp, frontal pole; O, occipital; P, parietal; and T, temporal.

The electrical potential recorded at an electrode on the scalp is the summed or superimposed signal of the postsynaptic electrical fields of similarly aligned neuronal dendrites. Recorded at the scalp as a waveform, the electrical potential has a particular voltage (which is a measure of its size) and a particular frequency, meaning that it

oscillates at a specific rate (measured in Hertz [Hz] or cycles per second). Clinically, EEG had been very helpful as it was used to detect epilepsy, which can be conceptualized as an electrical storm in the brain. Neurons normally fire in a synchronous manner. In epilepsy, however, rather than firing in a synchronous rhythm, neurons fire in large quantities at once (a burst, or “spike”) at random times. The result is an increase in the amplitude of firing that can be observed on the EEG record (see [Figure 2.6](#)). After an individual is treated with anticonvulsants, the EEG can be performed again to ensure that the spiking activity has decreased.

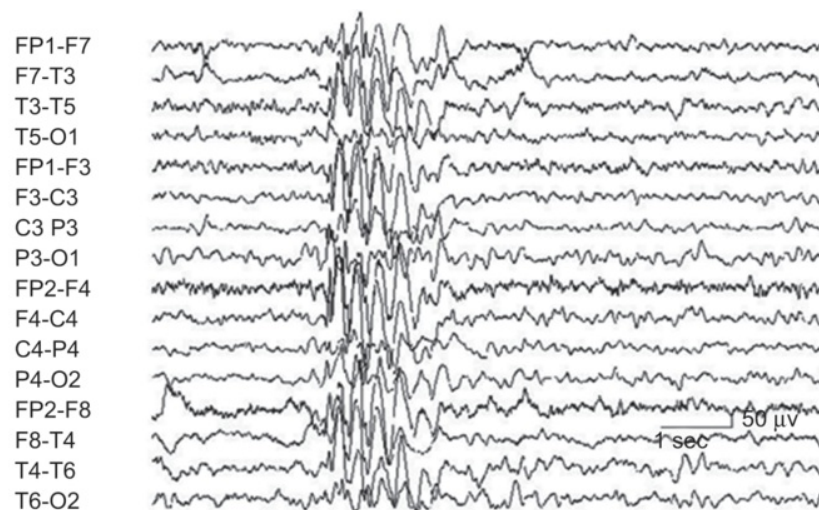


Figure 2.6 Electrical recordings of epileptic activity.

An example of the “spiking” activity that accompanies epilepsy, shown as a discrete increase in the voltage of the EEG. In this case, the seizure occurred over many regions of the brain simultaneously, as can be seen by the occurrence of high-voltage activity over all electrodes. The position of the electrode for each line of recording is indicated by the label to the left of the line.

(from <http://emedicine.medscape.com/article/1138154-overview>)

Scientists had also realized that EEG could be used to examine experimental questions because the frequency and form of the EEG signal vary according to a person’s state. During sleep, very slow frequencies of delta activity, at 1 to 4 Hz, predominate. When a person is relaxed, with his or her eyes closed, slower frequencies,

or alpha activity, at 9 to 12 Hz, are much more common. When a person is awake, the EEG shows a mixture of many frequencies, but those that are relatively fast (15 Hz), known as beta activity, tend to predominate (see [Figure 2.7](#)).

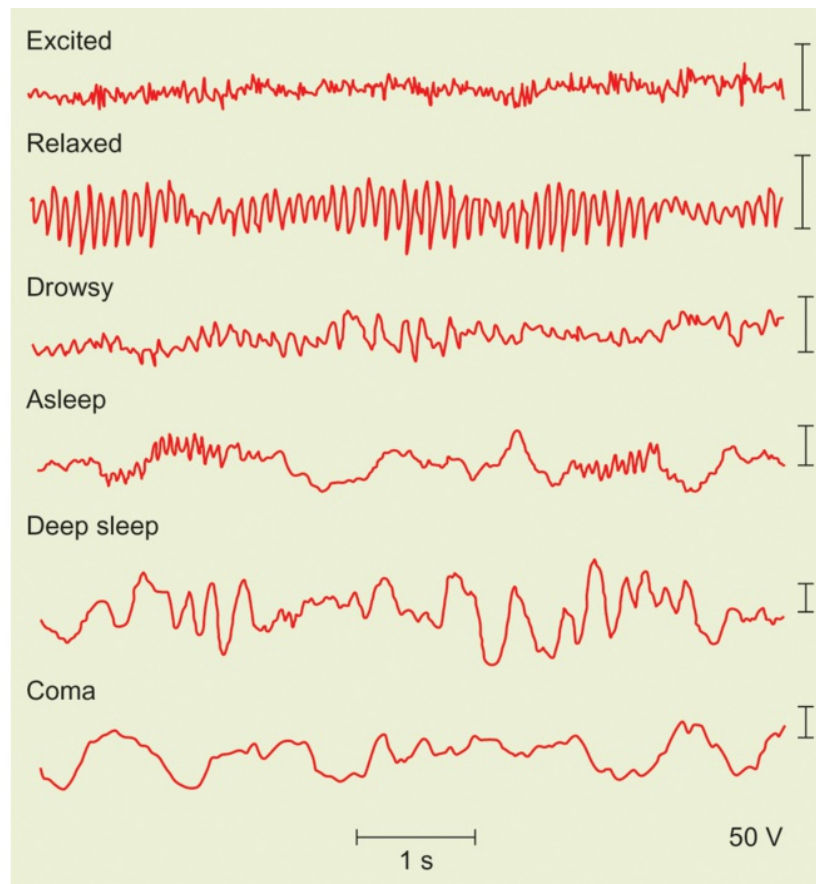


Figure 2.7 Examples of EEG recordings.

Characteristic EEG activity during various mental states. Note the cyclicity of activity that can be observed, for example, when an individual is in a relaxed state and how the frequency of that cyclicity is lower than when in an excited state.

Source: <http://emedicine.medscape.com/article/1138154-overview>.

For example, because alpha waves indicate that a person is relaxed and resting, the reduction of alpha activity, known as [alpha suppression](#), is often thought to indicate engagement in cognitive or emotional processing.

In the 1960s, computers helped to provide researchers with new and more effective ways to leverage electrical signals recorded from the brain. Whereas EEG recordings

provide a continuous measure of brain activity, [event-related potentials \(ERPs\)](#) are recorded in reference to a specific event. The common alignment and firing of dendritic fields in the brain after this event create a [dipole](#), which is a small region of electrical current with a relatively positive end and a relatively negative end (hence dipole, or two-pole, system). However, the size of the variation in the EEG signal that is induced by the event to form a dipole is quite small compared to the ongoing EEG signal. Therefore, detecting the ERPs requires signal averaging, in which the waveforms from multiple trials are averaged together (Galambos and Sheatz, [1962](#)) so that they can be revealed against variations in the EEG signal from trial to trial. Computers made such signal averaging possible.

Signal averaging, enabled by computers, revealed that as time from the onset of the stimulus elapses, the active groups of neurons, and hence the locations of the dipoles, change. Thus, the waveform recorded on the scalp changes as well. The waveform can be divided into [components](#), which are characteristic portions of the wave that have been linked to certain psychological processes, from early sensory processing in the brainstem to components associated with attention and memory. An example of a typical waveform with the different components is presented in [Figure 2.8](#). Therein lies their greatest strength: these components can offer some idea of when processes are occurring in the brain, providing important complementary information to other methods that provide insights as to where in the brain certain processes are localized.

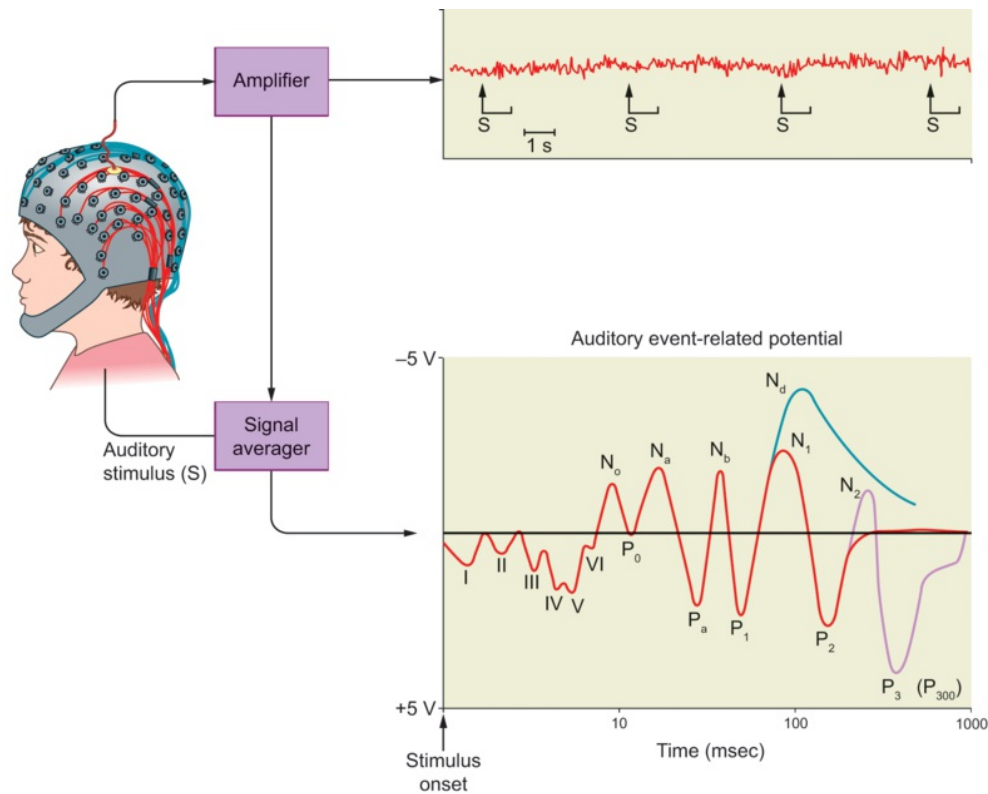


Figure 2.8 Components of an event-related potential.

The ongoing electroencephalography (top) is recorded from the scalp and passed through an amplifier. Every time a stimulus occurs (denoted by an S in the ongoing EEG), the electrical signal is recorded for a discrete period (e.g., 1 second). This is often referred to as “time-locked” because the recording is locked to a particular point in time. Signals from all such time periods (often a hundred or more) are then averaged, known as signal averaging, because ERPs are too small to be detected in the ongoing EEG. The resulting ERP from an auditory stimulus is shown below, with time plotted logarithmically to allow differentiation of the (N_0 , P_0 , N_a , P_a , N_b) responses from the brainstem (Waves I–VI) and early components (<100 ms post-presentation) that indicate the response of the brain to sensory characteristics of the stimulus as compared to later (P_1 , N_1 , P_2 , N_2 , P_3) components (>100 ms post-presentation) tend to be linked more to cognitive processes.

ERP components are usually given names that have two parts: a letter and then a subscript number (e.g., P_{300}). The letter is always a P or an N to denote whether the deflection of the electrical signal is positive or negative. The number represents, on

average, how many milliseconds (ms) after stimulus presentation the component appears. (Sometimes component names are abbreviated to represent, on average, how many hundreds of milliseconds after stimulus presentation they occur. In this case, for example, a P300 will be referred to as a P3.) This method of signal averaging “revealed the existence of novel, previously unknown, neural processes” (Donchin et al., [1978](#), p. 349). For example, the P300 component was discovered in 1965 (Sutton et al., [1965](#)), and was hypothesized to index a process related to uncertainty about incoming stimuli. In the [next chapter](#) we discuss in more detail the various ERP components and the mental processes to which we currently think they each are linked (see Chapter 3, pages [86–88](#)).

Disconnection Syndromes

So far we have been discussing behavioral functions as if they are localized to specific regions of the brain. But as we learned in the [last chapter](#), the brain consists of both gray matter (essentially the cell bodies of neurons) and white matter (the myelinated axons of neurons). In fact, white matter takes up so much of the brain that scientists sometimes refer to the “cortical ribbon” of gray matter that lies atop the large white-matter connective bundles (see [Figure 2.9](#)). Brain damage often is restricted to this cortical ribbon of gray matter, but also creates damage to the underlying myelinated axons, known as fibers of passage, that connect distinct brain regions.

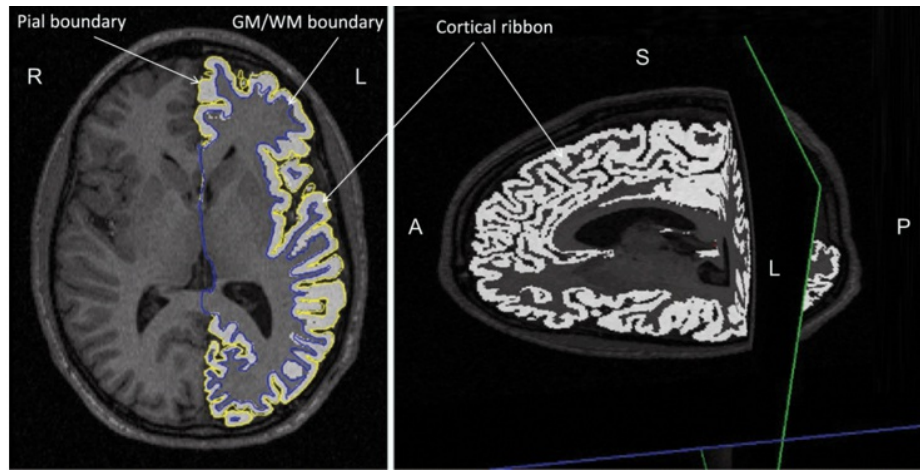


Figure 2.9 The thin cortical ribbon of gray matter that sits above the extensive amount of white matter that connects distant regions.

(A) Shown in an axial section; B) shown in a sagittal and coronal section. Notice that the gray matter sits above the white matter but below the pia mater (pial boundary), which is a thin membrane that surrounds the brain.

(from Sandu et al., [2014](#))

In some cases, behavioral deficits occur because a cognitive function relies critically on these white-matter tracts that connect disparate brain regions. Behavioral deficits that are caused by such damage are referred to as [disconnection syndromes](#). To understand this concept more clearly, consider the following analogy. Imagine we have a situation in which severe weather prevents food from the farms from reaching the city. Perhaps the farms were destroyed and are no longer producing food. This case would be similar to a brain lesion having damaged a portion of the gray matter critical for performance of a task. Alternatively, it may be that the farms are functioning normally but the highway between the farms and the city was washed out and ruined so that there is no route by which the food can be transported. This latter situation is similar to what occurs to white-matter tracts in a disconnection syndrome.

Throughout this book, we will discuss various examples of disconnection syndromes. One classic example is [conduction aphasia](#), in which an individual has a specific difficulty in repeating back what has just been said. In this syndrome the white-

matter tracts that connect Broca's and Wernicke's area are disrupted. As you just learned, Broca's area is important for producing speech output, while Wernicke's area is important for the comprehension of spoken language. When these two areas are disconnected, a person can comprehend language and can produce spoken language. However, she or he has difficulty repeating because what has just been heard cannot be fed forward to speech output areas for production (see Chapter 8, pages [288–289](#)).

In the 1960s, much of the earlier work examining disconnection syndromes was carefully laid out in two classic papers by the behavioral neurologist Norman Geschwind (Geschwind, [1965a](#), [1965b](#)). He argued that there were quite a number of syndromes besides conduction aphasia that could best be understood not as damage to specific brain regions that invoked specific processes, but rather as disconnections between brain regions, due to damaged white matter tracts, that kept different representations from being integrated (Catani and Ffytche, [2005](#)) (see [Figure 2.10](#)).

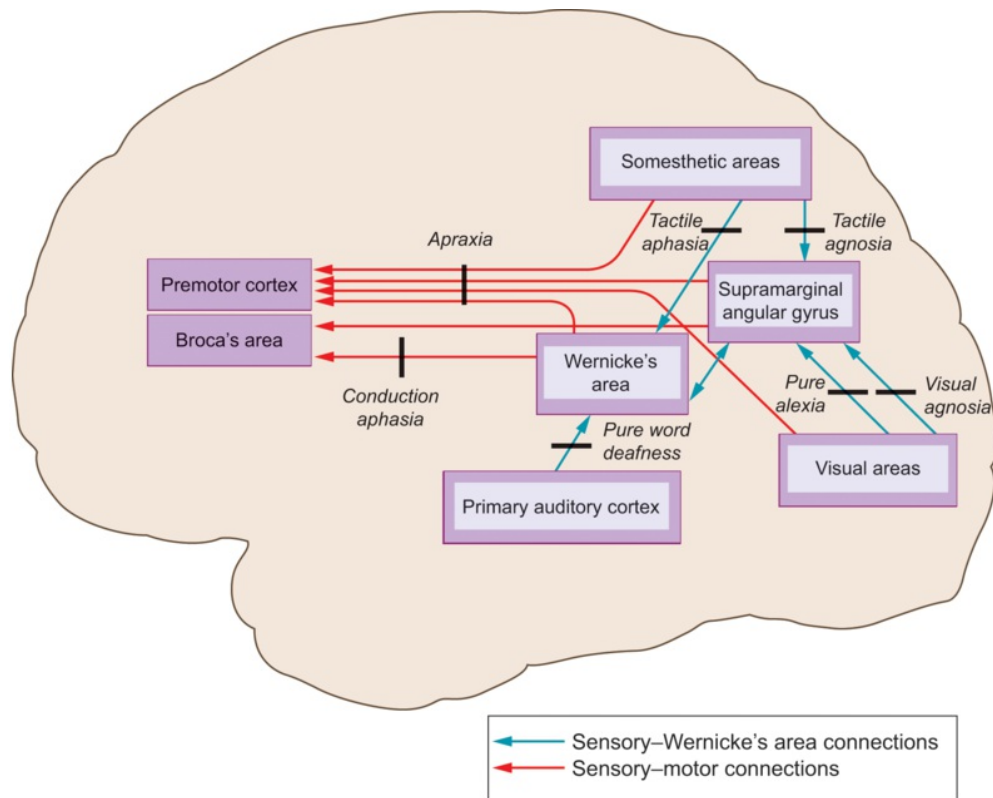


Figure 2.10 A diagram of numerous disconnection syndromes.

Shown here is a diagram of two sets of the disconnection syndromes classified by Geschwind: those that disconnect sensory and motor areas (red lines) and those that disconnect Wernicke's and other areas from sensory regions (blue lines). The disconnection syndrome is denoted by a black bar across the lines, with the behavioral syndrome positioned beside it (e.g., apraxia).

(from Catania and Ffytche, [2005](#))

The interest in disconnection syndromes in the mid-twentieth century in many ways was the precursor to the interest in brain connectivity that is an especially hot topic in cognitive neuroscience today. As we discussed in the [last chapter](#), brain function depends not only on regions specialized for certain functions, but also on the interaction between brain regions, as well as their organization into discrete subsystems, such as observed at rest (see pages [82](#), [84](#)).

Split-Brain Studies

Probably one of the most dramatic examples of what happens when brain regions are disconnected was exemplified by research in the 1960s by Roger Sperry and colleagues. Until this research, the function of the corpus callosum, the massive tract that connects the cerebral hemispheres, was unknown. To determine the function of the corpus callosum, Sperry and colleagues used a [split-brain procedure](#), so-called because it severs the primary route by which the left and right cerebral hemispheres interact, thereby splitting the brain in half. This procedure is also sometimes referred to as commissurotomy because it severs the corpus callosum, one of the brain's commissures (structures that connect the hemispheres).

While studying this structure in cats and monkeys, Sperry and colleagues determined the callosum was critical in the transfer of information between the brain's hemispheres (Sperry, [1961](#)). When the callosum is intact, the hemispheres can coordinate their processing, shuttling information back and forth with great speed over millions of nerve fibers. However, when the hemispheres are disconnected from one another, information is essentially trapped within a single hemisphere. Under such conditions the hemispheres appeared to sense, learn, and remember quite independently of one another!

The demonstration of this hemispheric independence was shown in a surgical preparation that involved severing not only the corpus callosum, but also the [optic chiasm](#). To better understand these studies, look at [Figure 2.11](#). As you may remember from [Chapter 1](#), information from the right eye projects both ipsilaterally and contralaterally. By severing the optic chiasm, visual input from a given eye was directed just to the ipsilateral hemisphere. By covering one eye (e.g., left), visual information would be projected to just one hemisphere (e.g., the right). The researchers then taught the animal, for example, a visual discrimination task, which it learned to a high degree of proficiency. Then to determine how much the other hemisphere had learned, the eye that had been open during initial learning was covered, and input was presented to the opposite, now uncovered, eye. Under these conditions, the animal showed what appeared to be complete amnesia for the task! This pattern was observed because what

the first hemisphere had learned could not be transferred to its partner. Studies such as these indicated that the corpus callosum is critical for transferring information between the hemispheres, and that each hemisphere can act as an independent and separate unit. These striking findings led researchers to ponder the idea of whether we have two minds residing within one brain.

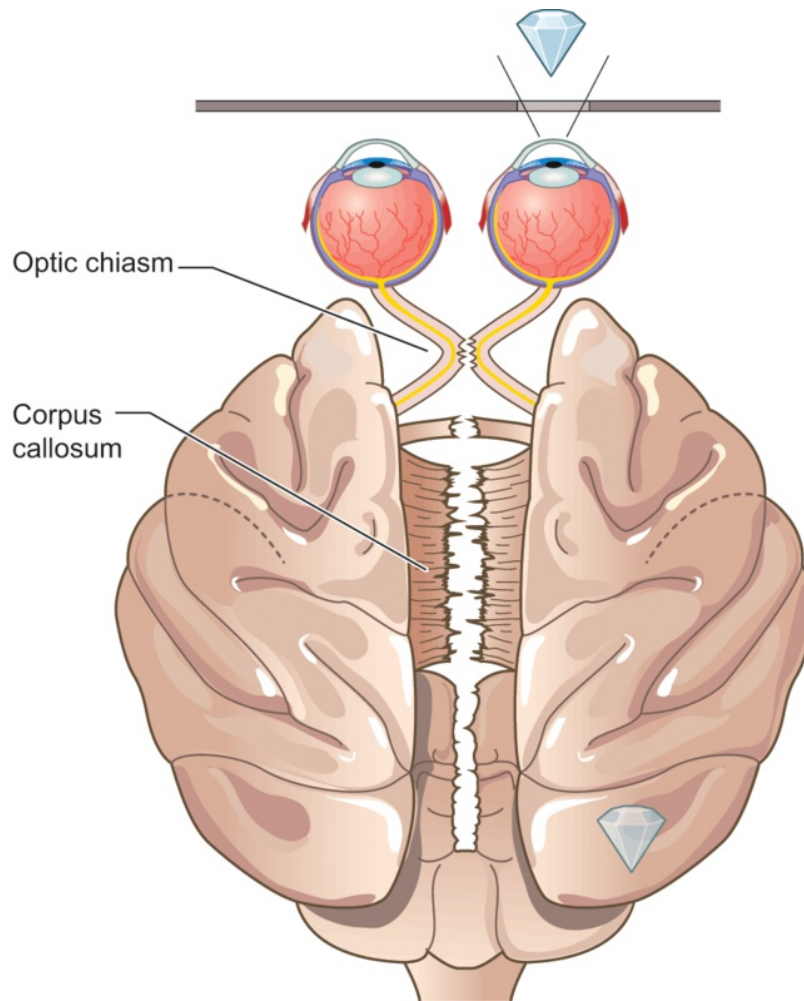


Figure 2.11 The split-brain preparation in the monkey.

To restrict information to just one hemisphere, both the corpus callosum and the optic chiasm were severed. In this manner, information presented to the ipsilateral eye went only to the ipsilateral hemisphere. Animals were taught simple tasks, like visual discrimination, in which information was restricted to one hemisphere by limiting visual information to just one eye, and thus one hemisphere. When the abilities of the opposite hemisphere were tested by now covering the eye used to learn the task, there appeared to be a total lack of knowledge, indicating that the corpus callosum is critical for transfer of information between the hemispheres.

Around the same time, the neurosurgeons Joseph Bogen and Philip Vogel were severing the corpus callosum in a small group of people for a different reason: to control intractable epileptic seizures. These patients' seizures did not diminish with anticonvulsant medication and were so frequent and severe as to make any semblance of

a normal life impossible. A callosotomy appeared to keep the number of misfiring nerve cells from reaching a critical mass because cells from the opposite hemisphere could not be recruited, thus alleviating their devastating seizures.

These neurosurgeons teamed together with Sperry and his associates to determine whether the callosum plays a similar role in humans. These investigations were a tad more complicated, however, because, for obvious reasons, the optic chiasm was not also severed as part of the split-brain surgery. This required the experimenters to devise methods that would take advantage of the neuroanatomy of the human nervous system, so as to enable them to direct information to only one hemisphere at a time. In the [divided visual field technique](#), a participant is told to maintain fixation on a central point. While they are doing so, information is presented laterally (at least 1 or 2 degrees) from midline for 200 milliseconds (one-fifth of a second) or less. Since it requires about 200 ms to move one's eyes, if the person has been fixating centrally, then as we learned in Chapter 1 (see [Figure 1.24](#), page 30) information to the right of fixation (i.e., in the right visual field) will project to the left hemisphere and information to the left of fixation (i.e., in the left visual field) will project to the right hemisphere. Consistent with animal research, when information was presented visually to the left hemisphere, the right hemisphere was clueless as to what its partner had just seen, and vice versa. Thus, it was proven that the corpus callosum is critical for information transfer between the hemispheres.

Hemispheric Specialization: Left Brain, Right Brain

Another astounding scientific opportunity was provided by split-brain patients: the ability to test the competency of each hemisphere in isolation separated from its partner. Scientists were already aware that the cerebral hemispheres were not equivalent. The difference in processing between the hemispheres is often referred to as [hemispheric specialization](#), or [lateralization of function](#). As we noted, in the latter half of the nineteenth century, Broca, Wernicke, and others had found that language abilities were specifically impaired after left-hemisphere lesions. Around the same time, some

neurologists, such as John Hughlings Jackson, argued that damage to the right hemisphere led to somewhat different consequences, more specifically with regards to aspects of spatial processing, as well as emotion processing (see Harris, [1999](#) for historical review). Furthermore, neuroanatomists had noted that while mainly symmetrical, there were important asymmetries in brain anatomy (see Toga and Thompson, [2003](#), for review).

Testing the Isolated Hemispheres

Split-brain patients provided an important new way to examine these asymmetries. Rather than making inferences based on the loss of function, there was the ability to test each relatively intact hemisphere within the same person. One of Sperry's first goals was to determine lateralization of speech output in the split-brain patients, as language had been thought since Broca's time to be lateralized to the left hemisphere. Sperry and his colleagues asked the patients to feel objects with just one hand, either just the left or just the right. The objects were hidden from view so that the only source of information about them was tactile. With this procedure, objects felt by a given hand are perceived exclusively by the contralateral hemisphere. Thus, objects felt by the right hand of a patient with the split-brain syndrome would be perceived only by the left hemisphere and those felt by the left hand would be perceived only by the right hemisphere. Strikingly, patients were able to name the objects placed in the right hand but not those placed in the left.

Did the object in the left hand go unreported because the right hemisphere did not understand what the object was? Or was the right hemisphere unable to verbalize what it understood? To distinguish between these possibilities, the researchers changed the task so that the patient had to demonstrate the correct use of familiar objects, such as pencils, cigarettes, and drinking glasses. The researchers found that objects placed in the left hand could be used correctly, an indication that the right hemisphere can demonstrate its knowledge of the object nonverbally even though it is mute (Gazzaniga et al., [1962](#)).

These findings were consistent with reports coming from research associated with surgical patients about to undergo tissue removal to control epileptic seizures. Prior to commencing surgery, the surgeon wants to know which hemisphere is dominant for language. To do so they utilized a procedure, called the [Wada technique](#), that is used to this day to determine which hemisphere is responsible for speech output in patients. In the Wada technique, illustrated in [Figure 2.12](#), a person is lying on his or her back on a table with arms and knees up. Then a barbiturate (typically sodium amobarbital) is injected into one of the carotid arteries that lead from the heart to the brain. Because the blood supply from the heart to the brain is unilateral, the barbiturate initially anesthetizes only one hemisphere. If the person is mute and unable to speak, the anesthetized hemisphere is inferred to be involved in speech output (Wada and Rasmussen, [1960](#)). Research with this method has revealed that the left hemisphere is dominant for speech in 95% of right-handers, a finding consistent with evidence from patients who sustain unilateral brain damage (Rasmussen and Milner, [1977](#)).

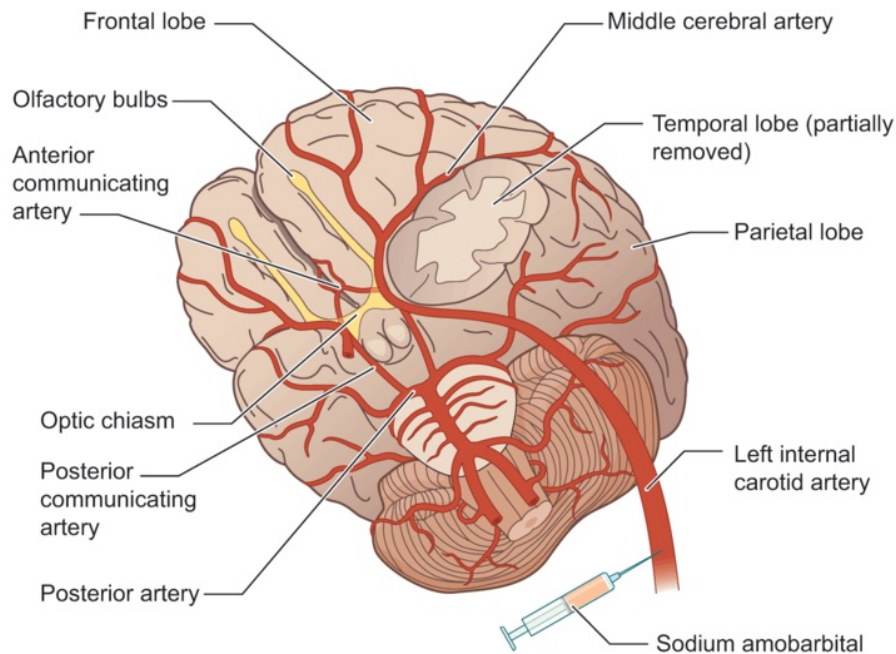


Figure 2.12 The Wada technique to assess cerebral lateralization of language prior to surgery for epilepsy.

In this technique a barbiturate, typically sodium amobarbital, is introduced to the brain (as seen from below) via one of the two internal carotid arteries (in this case the left). Due to the nature of the blood supply to the brain the barbiturate first courses through the hemisphere supplied by that internal carotid artery, resulting in paralysis on the contralateral side of the body (e.g., right). At this point with paralysis indicating that the barbiturate has taken effect, medical personnel determine whether speech output and other aspects of language processing are possible. Within 5–10 minutes, the barbiturate diffuses to the opposite hemisphere via the anterior and posterior communicating arteries, and tests for lateralization of speech output can no longer be performed.

The researchers then probed whether the right hemisphere had any language at all. While the right hemisphere is much more than a spare tire, research with split-brain patients indicates its linguistic capacity is somewhat limited (for debate regarding degree see Gazzaniga, [1983a](#), [1983b](#); Levy, [1983](#); Zaidel, [1983a](#)). First, as we have already learned, the right hemisphere cannot control speech output. Second, it cannot understand complicated grammatical constructions (e.g., “The dog that the cat chased

ran under the table behind the garage that was condemned by the sheriff last week”) (Zaidel, [1978](#)). Rather, its grammatical abilities are limited to simple distinctions (e.g., differentiating between “The boy went to the store” and “The boy did not go to the store”), and its vocabulary is limited mainly to concrete words (i.e., words that represent real objects or actions) (e.g., Zaidel, [1990](#)). Finally, the right hemisphere seems unable to break words down into their constituent sounds, a task known as phonologic processing, which is required to determine whether two words rhyme (e.g., Levy and Trevarthen, [1977](#)).

Because the right hemisphere’s language capability was revealed to be relatively poor in split-brain patients, researchers began to focus their attention on what the right hemisphere could do. Additional experiments demonstrated that the right hemisphere excels at spatial or nonverbal tasks. For example, when given a task in which blocks must be arranged to form a pattern, the right hand performed in a hapless and disorganized manner. In contrast, the left hand performed the task rapidly and accurately. In addition, the left hand, but not the right, could depict three-dimensional structures in a two-dimensional plane, such as drawing a cube on a piece of paper (Gazzaniga, [1970](#)).

Other studies revealed that the right hemisphere was superior on spatial tasks even when no manual manipulation was required. In a series of studies, patients with split-brain syndrome were asked to view chimeric faces (i.e., faces composed of two different sides, such as those in [Figure 2.13](#)). Although these figures seem strange to us, remember that the hemispheres of a split-brain patient cannot communicate, so they do not realize that they are viewing different faces. When split-brain patients were asked to point to the face that had been shown, accuracy was much greater with the left hand than the right hand. This pattern held not only for faces but also for abstract forms (Levy et al., [1972](#)). Therefore, the results of research on patients with split-brain syndrome suggested the complementarity of the hemispheres for different aspects of mental functioning, with the left being superior at processing verbal material, while the right is superior in the spatial domain.

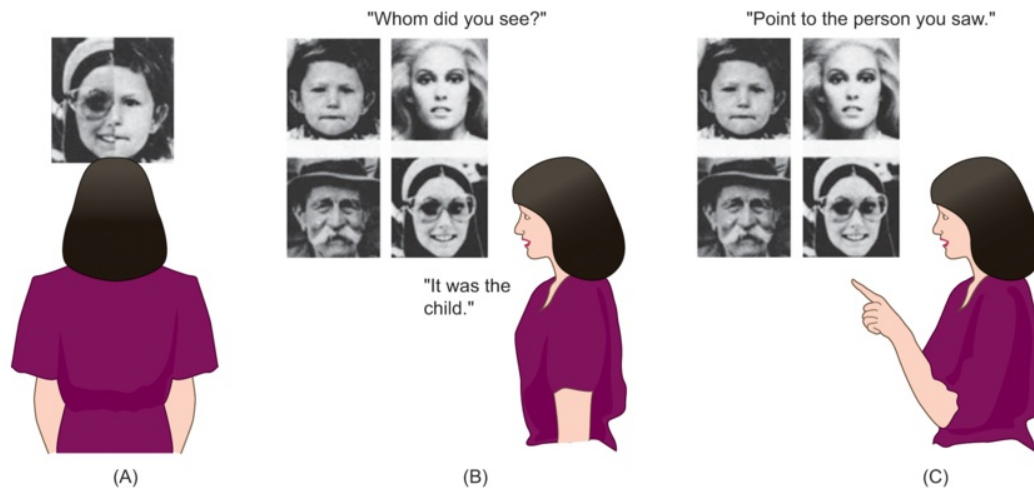


Figure 2.13 Examining the competency of each hemisphere in a patient with the split-brain syndrome.

(A) An example of a chimeric stimulus, composed of two half-faces that are perceived by opposite hemispheres. Although these figures look strange to us, they do not look so to split-brain patients, who when fixated on a central location, are not aware of the difference in what each hemisphere is viewing. (B) When asked to report verbally which face was seen, the patient reports the face that was seen by the left hemisphere (right visual field). (C) When asked to point with the left hand to the face that was seen, the patient points to the face that was seen by the right hemisphere (left visual field). Accuracy is higher when pointing with the left hand to the face seen in the left visual field, compared to pointing with the right hand to the face seen in the right visual field. This finding indicates a right-hemisphere superiority for face recognition.

Source: Reception of bilateral chimeric figures following hemispheric deconnexion, Levy J., Trevarthen C., Sperry, R. W. *Brain*. 1972; 95(1): 61–78. By permission of Oxford University Press.

Because studies of patients with split-brain syndrome provide information on the functioning of a reasonably intact but isolated hemisphere, they have been and continue to be a powerful tool in our attempts to understand asymmetry of function in the human brain (see Gazzaniga, 2005).

Research With Individuals Who Have Lateralized Lesions

While dramatic demonstrations of lateralization of function were being provided by split-brain research, studies with other neurological patients were also revealing the distinct capabilities of the hemispheres. Although scientists had known for some time that left-hemisphere lesions compromise language functioning, other methods provided converging evidence.

Studies of patients with brain damage have also demonstrated that right-hemisphere lesions have different consequences than left-hemisphere lesions. Whereas left-hemisphere lesions disrupt language-related processing, right-hemisphere lesions disrupt many spatial and visuospatial abilities. For example, individuals with right-hemisphere damage are poor at making judgments about line orientation (Benton et al., [1975](#)), have difficulty recognizing objects that are not in a standard or canonical form (Warrington and Taylor, [1973](#)), and are poor at distinguishing between faces that were previously viewed and those that were not (Yin, [1970](#)). In addition, patients with right-hemisphere damage have difficulty distinguishing different pitches of sound or tones of voice (Ross, [1981](#)) and cannot interpret the emotional expression of faces (Bowers et al., [1985](#)). This body of research revealed that the right hemisphere has cognitive abilities just as sophisticated as those of the left hemisphere, albeit in nonverbal, nonlinguistic domains.

Research With Neurologically Intact Individuals

With these discoveries, there was a veritable torrent of research for over a decade that focused on examining and elucidating hemispheric differences. This work proliferated, in part, because it is relatively easy to examine hemispheric differences in neurologically intact people, as in most sensory modalities, information from one sensory half-world is directed initially to the primary sensory regions of the opposite hemisphere. The large body of evidence garnered in this manner provides a third converging approach that illustrates the specialization of the hemispheres for different

cognitive and emotional processes. Before discussing this evidence further, though, we first discuss the methods used to investigate lateralization of function.

The general logic of these experiments was to pit the hemispheres in competition with one another and see which one excelled at processing. This was accomplished by presenting information to each hemisphere separately, or in some cases simultaneously. In the visual modality, the divided visual technique that we discussed above in regards to split-brain research was used. A related technique is used to present information in the auditory modality, although it was a bit more complicated. As you may remember from [Chapter 1](#), information from each ear connects both to the primary auditory cortex of the contralateral hemisphere and to the primary auditory cortex of the ipsilateral hemisphere. Under special conditions known as [dichotic presentation](#), the situation is simplified (see [Figure 2.14](#)). In dichotic presentation, different information is presented simultaneously to each ear so that each hemisphere receives two competing pieces of information, one from the ipsilateral ear and one from the contralateral ear. Because of this competition, information traveling to a hemisphere from the ipsilateral ear is suppressed relative to information from the contralateral ear (Milner et al., [1968](#)). Thus, information from the right ear is processed almost entirely by the left hemisphere and information from the left ear is processed almost entirely by the right hemisphere.

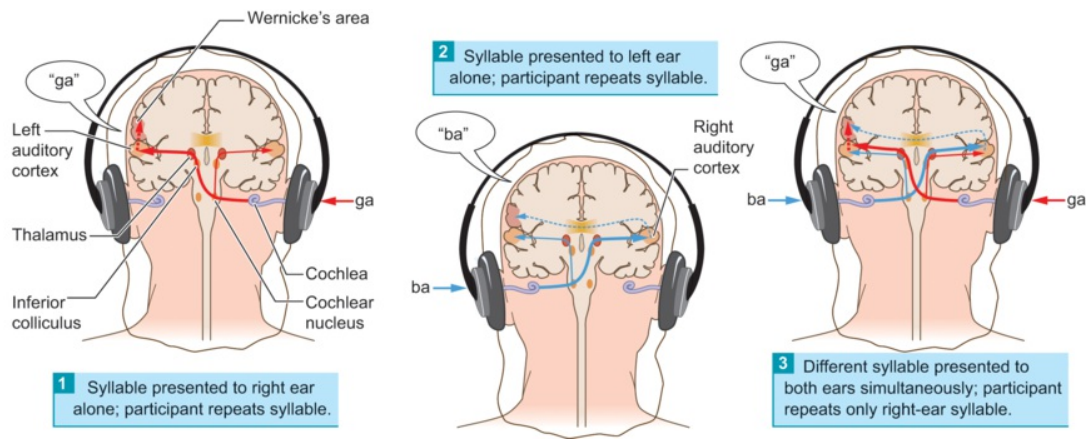


Figure 2.14 Ipsilateral suppression in the dichotic listening technique.

When a syllable is presented to either the right or to the left ear (monaural stimulation), the person can easily report the syllable. The auditory information from each ear is sent to both hemispheres via both contralateral and ipsilateral connections. However, when the two ears are simultaneously stimulated with different syllables (dichotic stimulation), people typically have trouble reporting both syllables. Under dichotic conditions, the syllable presented to the right ear is usually reported more accurately than the syllable presented to the left ear, because the right-ear syllable has better access to the verbal left hemisphere. The syllable presented to the left ear is not reported as well because information carried through ipsilateral fibers is suppressed under dichotic conditions, and therefore the left hemisphere does not have direct access to the left-ear syllable.

We can infer how well each hemisphere processes information by comparing either the speed or the accuracy of performance for items presented in the right visual field (RVF) (or right ear) versus the left visual field (LVF) (or left ear). For example, if recall of information is superior when presented in the RVF than when presented in the LVF, the left hemisphere is assumed to be specialized for processing that type of information. Note that what we actually observe is an asymmetry in the perception of information depending on which part of the sensory system we stimulate; these differences in performance are therefore often referred to as **perceptual asymmetries**. Because different parts of the sensory system project to different hemispheres, the perceptual asymmetries are interpreted as reflecting hemispheric differences.

Studies examining perceptual asymmetries have been quite effective in revealing differences in the processing capabilities of the hemispheres. As you might expect based on what you have already learned, processing of verbal materials tends to be superior when directed initially to primary sensory regions of the left hemisphere, whereas nonverbal information tends to be processed better when directed initially to the right hemisphere. For example, in the visual modality, studies usually find a RVF (or left-hemisphere) advantage for words and a LVF (or right-hemisphere) advantage for faces (Levine and Banich, [1982](#); Levine et al., [1988](#)). In the tactile modality, a right-hand advantage is found for identifying letters drawn on the palm (e.g., O'Boyle et al., [1987](#)) and for identifying dichaptically presented letters made of sandpaper (Gibson and Bryden, [1983](#)). In contrast, when individuals must feel two complex shapes simultaneously and match them to a visual array or otherwise identify them, a left-hand advantage appears (Gibson and Bryden, [1983](#); Witelson, [1974](#)). In the auditory modality, the response to words and other speech sounds is better when the sounds are presented to the right ear (e.g., Kimura, [1967](#); Studdert-Kennedy and Shankweiler, [1970](#)), whereas response to nonverbal sounds, such as animal noises, environmental sounds (e.g., doors opening, train whistles), and musical tones, is more accurate when the material is presented to the left ear (e.g., Gordon, [1980](#)). These advantages are typically small, on the order of a 10% difference in accuracy or 20- to 30-ms difference in reaction time. They are nonetheless impressive considering that the hemispheres are connected by the 250 million nerve fibers of the corpus callosum.

How do such perceptual asymmetries arise in neurologically intact people, given the vast network of interconnections between the hemispheres? No single account is agreed upon, but researchers have a number of ideas. One idea, referred to as the [direct access theory](#), assumes that the hemisphere receiving sensory information processes it. When information is received by the hemisphere less suited to a task, performance is poorer than if it is received by the hemisphere better suited to the task. Another idea, the [callosal relay model](#), assumes that information received by the hemisphere less adept at a given task is transferred to the opposite hemisphere. This callosal transfer degrades

the information and leads to poorer performance than if the information is received by the hemisphere more suited to the task (see Zaidel, [1983b](#), for a discussion of these issues). A third type of model, known as the [activating-orienting model](#), suggests that an attentional set or bias can contribute to perceptual asymmetries (Kinsbourne, 1974). According to this theory, engaging in a particular type of process (e.g., word recognition) causes greater activation in the hemisphere best suited to the task (e.g., the left hemisphere). This increased activity is thought to result in an attentional bias to the side of space contralateral to the more active hemisphere (i.e., the right side). As a result, perceptual information on that side of space is more salient, allowing it to be processed better.

Theoretical Conceptions of Hemispheric Differences

So far, we have emphasized the viewpoint that the hemispheres are specialized for processing different types of material: verbal versus nonverbal. One of the major conceptual breakthroughs in the field was to posit that the hemispheres differ not so much in what type of information they process, but rather in how they process information (Levy et al., [1972](#)). This idea was proposed based on research in which split-brain patients were shown chimeric faces, such as those discussed earlier. Even though the right hemisphere was superior at identifying faces, some interesting results emerged. The performance of the left hemisphere on face recognition could be improved by focusing in on details of the face (see [Figure 2.15](#)). When giving a vocal response (controlled by the left hemisphere) performance improved after training in which the patient was taught that “Dick wears glasses” and “Bob has a moustache.”

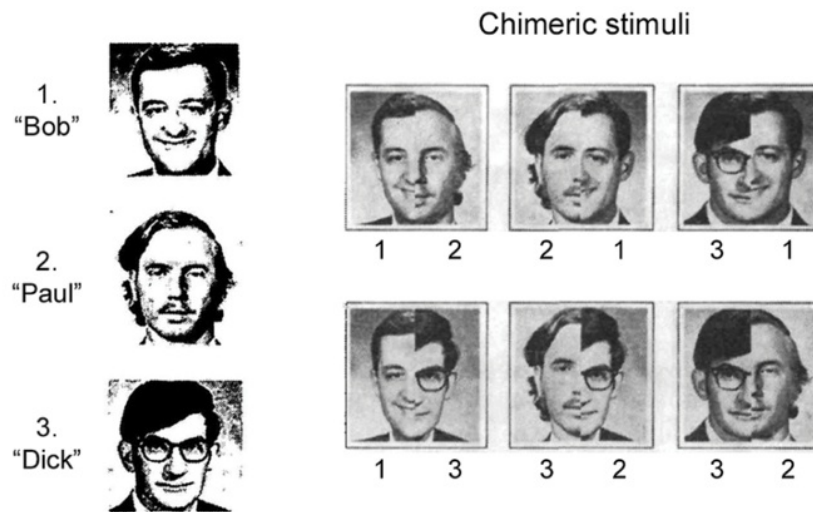


Figure 2.15 Example of chimeric stimuli that helped to illustrate that the hemispheres differ in the manner by which they process information, not necessarily whether the content is verbal or nonverbal.

Although the right hemisphere is superior at face recognition, performance of the left hemisphere could be boosted if the left hemisphere was taught to focus in on details such as that "Paul has a moustache" and that "Bob wears glasses".

(from Levy et al., [1972](#))

As a result, researchers suggested that the hemispheres have different modes of processing and that these two distinct modes provide complementary information about the world. In particular, the left hemisphere processes information in a piecemeal and analytic fashion, with a special emphasis on temporal relationships; the right hemisphere is thought to process information in a gestalt and holistic fashion, with a special emphasis on spatial relationships.

These different modes of processing can be observed by comparing the performance of patients with unilateral damage to either the left or right hemisphere. For example, look at the figures in [Figure 2.16](#), which are often referred to as hierarchically organized figures. After sustaining a right-hemisphere lesion, patients have difficulty paying attention to the global form of the item (i.e., an M or a triangle) but have no difficulty paying attention to the local pieces or parts (i.e., the Zs or the rectangles). Conversely, after left-hemisphere damage, patients have difficulty paying attention to the

parts (i.e., the Zs and the rectangles) but no difficulty with the global form (i.e., the M and the triangle) (Robertson and Lamb, [1991](#)). Regardless of whether the stimulus is linguistic or nonlinguistic, the hemispheres take complementary roles in processing. Metaphorically, the right hemisphere pays attention to the forest while the left hemisphere pays attention to the trees.

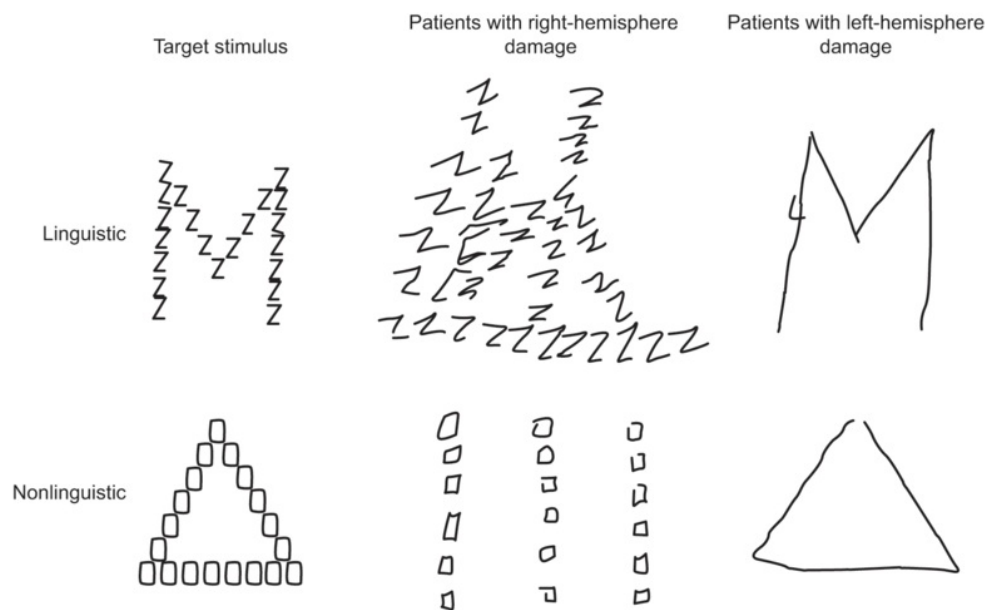


Figure 2.16 Hemispheric differences between global and local processing.

Patients who sustain damage to the right hemisphere can correctly draw the local, or component, parts of the objects, as illustrated by the correct drawing of the Zs and the rectangles. However, the overall global form is incorrect; it is neither an M (in the case of the linguistic stimulus) nor a triangle (in the case of the nonlinguistic stimulus). In contrast, patients who sustain damage to the left hemisphere can correctly draw the global form of the items but not the local, or component, parts.

Generally, researchers agree that both hemispheres contribute simultaneously to performance on almost all tasks, albeit in different manners (e.g., Beeman and Chiarello, [1998a](#), [1998b](#); Chabris and Kosslyn, [1998](#); Ivry and Robertson, [1998](#); Robertson and Ivry, [2000](#)). This makes sense: it means that the right hemisphere is not just taking a nap while we are reading, and the left hemisphere is not just snoozing while we recognize a friend's face. Going around in such a half-brained manner doesn't

seem a very good strategy! Instead, each hemisphere contributes in some way to nearly all complex mental functions. Even those functions traditionally thought of as relying on one hemisphere, such as verbal and spatial abilities, actually seem to intimately involve both hemispheres. This idea will be discussed many times through the text.

In Focus: Left Out? Lateralization in Non-Right-Handers

Scientists have known for some time that the brain organization for left-handed individuals is distinct from that for right-handed individuals. Historically, left-handers have been characterized in a none-too-flattering way. For example, the Latin word for left is sinister, whereas the French word is gauche. In certain cultures, such as in India, the left hand is never used to eat a meal (nor is it extended to someone for a handshake) because it is the hand reserved for less pleasant functions. Even in the early to mid-twentieth century, individuals who wrote with the left hand were considered evil, stubborn, and defiant, and consequently they were often forced to write with the “correct” (right) hand (see McManus, [2002](#), for a fascinating discussion of left and right in cultures and nature). Left-handers often were subjected to such indignities because they are a minority, and in the past were often forced to perform manual tasks with the right hand. When such cultural restrictions are removed, the best estimates generally suggest that they represent around 10% of the population (Perelle and Ehrman, [1994](#)).

Left-handers have often taken solace in the face of such unfair negative stereotypes by the fact that notable individuals such as Leonardi di Vinci were left-handed. And at least some initial studies suggested that amongst intellectually gifted individuals there is a higher proportion of left-handers (Ehrman and Perelle, [1983](#)), although more recent evidence does not support such an assertion (Papadatou-Pastou and Tomprou, [2015](#)). In fact, one of the authors grew up right-handed in an extended family of left-handers, leaving her

feeling mundane and ordinary among her self-professed “smarter” and more “creative” relatives. This experience, in fact, helped to propel her into studying cognitive neuroscience as she discovered in an introductory psychology class that indeed left-handers are “special” in that their brain organization differs from that of right-handers (see biography in Gorvine et al., [2017](#)).

As we mentioned earlier, classic work using the Wada technique indicates that speech output is not always lateralized to the left hemisphere. Among left-handers, 70% have speech controlled by the left hemisphere, 15% by the right, and 15% by either hemisphere (Rasmussen and Milner, [1977](#)). When we average across all these types of left-handers, as a group they appear to be less strongly lateralized than right-handers (Bryden, [1965](#); Hécaen et al., [1981](#)). In addition, there may be a smaller degree of lateralization within a given left-handed person compared to a right-handed person. The brains of left-handers do not show as strong anatomical asymmetries in brain regions such as the [planum temporale](#), which is important for language comprehension (Geschwind and Letvisky, [1968](#); Steinmetz et al., [1989](#)). Moreover, the degree of the anatomical asymmetry predicts the degree of hemispheric asymmetry in brain activation when listening to stories (Tzourio et al., [1998](#)). And left-handers do not show as strong a lateralization of function for the processing of visuospatial materials such as faces and bodies (Willems et al., [2010](#)). And if you are a right-hander, having a left-handed relative may influence your brain organization, with more left-handed relatives and a left-handed mother being most associated with reduced asymmetry of the planum temporale (Tzourio-Mazoyer, Simon et al., [2010](#)). In addition, right-handers with a family history of sinistrality show less of a bias toward asymmetric activation of the left hemisphere during a language comprehension task (Tzourio-Mazoyer, Petit et al., [2010](#)).

Because on average left-handers are less lateralized than right-handers, it had been thought that the consequences of brain injury for a given function may

not be as dire for left-handers. For example, after damage to the left hemisphere, left-handers had been found to exhibit less severe language deficits than right-handers, because it was hypothesized that language output may be controlled by one hemisphere and language comprehension by the other (e.g., Naeser and Borod, [1986](#)). Yet, this reduced lateralization has converse consequences. Following left-hemisphere damage, left-handers were shown to exhibit more severe visuospatial deficits than right-handers (Borod et al., [1985](#)). However, more recent meta-analyses do not find that handedness is an important predictor of recovery of language function after stroke, which not surprisingly is determined more by lesion size and location (Watila and Balarabe, [2015](#)). Nonetheless, such findings do not preclude the possibility that the specific pattern of language deficits after injury might not differ between left-handers, right-handers with left-handed relatives, and right-handers with right-handed relatives. But more research will be needed to investigate this possibility.

One of the difficulties in current neuroimaging research is that, for the most part, studies have excluded left-handers from participation, with the rationale that they add “noise” to the data, obscuring basic fundamental patterns of brain organization. However, the exclusion of left-handers from such studies may be counterproductive, precluding us from obtaining a better understanding of brain organization (Willems et al., [2014](#)). For example, in practically all right-handers, language is lateralized to the left hemisphere and visuospatial abilities to the right, so as to preclude a determination as whether these two types of lateralization are always opposed to each other. Only by observing that there are left-handers with language organized to the right hemisphere who also have visuospatial abilities organized to the left hemisphere does a reciprocal relationship between language and visuospatial abilities become clear (Cai et al., [2013](#)).

The biological mechanisms leading to left-handedness and cerebral asymmetry itself remain obscure. While it was thought at one time that there

might be a single gene that would bias toward left-hemisphere dominance for language and right-handedness (Annett, [1985](#), [1995](#)), more advanced genetic analysis suggests that handedness is a polygenic trait, that is, one that occurs due to the influence of a large number of different genes (Somers et al., [2015](#)). And a study of over 25,000 Australian and Dutch twin families suggests that handedness, while partially due to genetic factors, is also influenced by nongenetic factors as well (Medland et al., [2009](#)). In addition, debate continues as to why having an asymmetric nervous system and brain might be useful. Some theories suggest that by dividing processing across the hemispheres, two objectives can be met at once: one system controls behavior that aids in eating and the other controls behaviors that help an organism avoid being eaten! For example, the right hemisphere appears to be specialized for predator detection and escape behaviors, whereas the left hemisphere is specialized for prey catching and foraging (Vallortigara and Rogers, [2005](#)). With regards to humans, another viewpoint suggests that lateralization in humans may have been advantageous because it allowed for the best expression of complex manual or vocal skills that are crucial for communication to be organized to a single hemisphere (Corballis, [2012](#)). So, if you enjoy pondering the mysteries of lateralization of function, are one of those 10% of people who is left-handed, or one of the 30% of the right-handed individuals with a left-handed relative, you can raise your glass and toast to those intriguing sinistrals on August 13th, International Left-handers Day!

Integration of Information Between the Hemispheres

Before we leave the topic of hemispheric specialization, it is important to remember that our actions and everyday experiences reflect the unified processing of a single brain, not the output of two distinct minds. Thus, we must address the question of how the hemispheres communicate with each other and coordinate processing to yield a

seamless response. We focus here on two aspects of this issue. First, we examine the properties of the corpus callosum, the main conduit through which the hemispheres communicate, and then we examine whether interhemispheric interaction serves any other additional purposes besides keeping the two hemispheres coordinated.

As we mentioned earlier, the corpus callosum consists of over 250 million nerve fibers. In general, homologous regions of each hemisphere are connected to one another (refer back to [Figure 1.30](#)). As such, there is an orderly structural organization to the callosum. Anterior sections of the callosum connect anterior sections of the brain, and posterior sections of the callosum connect posterior sections of the brain. Because of this organization, different types of information are transferred across different parts of the callosum depending on the brain regions connected by that section of the callosum. For example, information about motor signals is transferred in the middle of the callosum (known as the body), whereas visual information is transferred in the back of the callosum (a region known as the splenium). As determined from electrical recordings, information in the largest myelinated fibers can course from one hemisphere to the other in as little as 5–20 milliseconds (e.g., Saron and Davidson, [1989](#)) (see [Figure 2.17](#)).

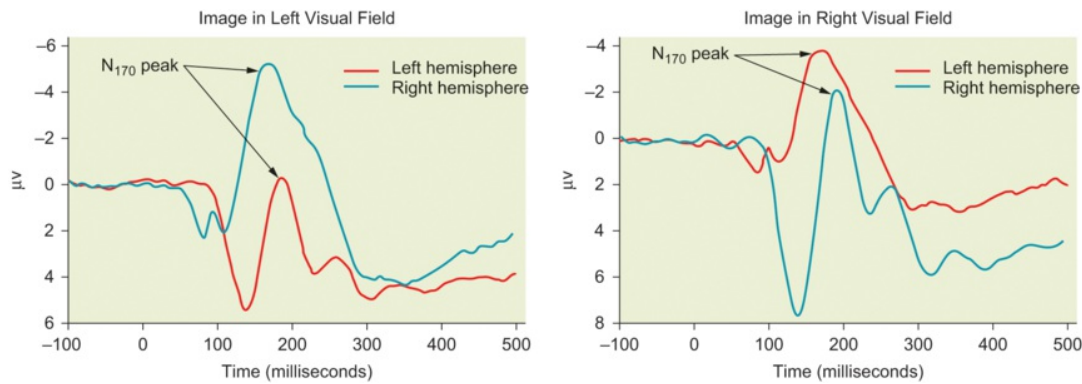


Figure 2.17 The rapid transfer of sensory information from one hemisphere to the other.

Shown here are event-related potentials (ERPs) evoked by images of faces presented in either the left or right visual field. The waveforms were recorded over the temporal lobes of both hemispheres. The N170 peak in the waveform occurs sooner over the hemisphere that directly receives the visual information (the contralateral hemisphere), compared to the hemisphere that receives the information only after it is transferred across the corpus callosum. For example, a face image that is presented to the left visual field will evoke an N170 peak sooner over the right hemisphere than the left hemisphere, and vice versa. The time it takes for information to be sent over the callosum is estimated by the time difference between the left- and right-hemisphere peaks, approximately 15 to 20 milliseconds.

While there are other commissures that transfer information between the hemispheres, the corpus callosum is required to transfer higher-order information. Studies with split-brain patients have revealed that detailed information required to uniquely identify an item can be transferred between the hemispheres only by the callosum, although more general information can be transferred through subcortical commissures (see Gazzaniga, [2000](#), for a review). For example, patients with split-brain syndrome cannot determine whether two faces, each directed to a different hemisphere, are the same person (e.g., whether the face that each hemisphere is viewing is Madonna). However, the subcortical commissures may be able to transfer some dichotomous information, such as whether the face is of a younger or older adult, is a female or a male, or is an emotionally negative or positive image (Sergent, [1990](#);

Sperry et al., [1979](#)). From these studies we can conclude that the corpus callosum is the major conduit for transfer of higher-order information between the hemispheres, but that other brain commissures are capable of transferring basic and rudimentary information.

However, research also pointed to another important role of interhemispheric interaction, which is in accord with recent trends to consider the action of the brain as a coordinated system. In particular, interhemispheric interaction may enhance the overall processing capacity of the brain under highly demanding conditions (see Banich, [1998](#), [2003](#), for a review). Demanding conditions include those in which processing is relatively complex, when information must be simultaneously processed within a short period, or when a task is difficult because of the need to ignore other information that is distracting or irrelevant.

To examine how interaction between the hemispheres enhances the brain's capacity to process information, two types of trials are contrasted (see [Figure 2.18](#)). In some trials (called across-hemisphere trials), critical items are directed to opposite hemispheres and have to be compared; in other trials (called within-hemisphere trials), the critical items are directed initially to just one hemisphere. Across-hemisphere trials require interhemispheric communication, whereas within-hemisphere trials do not. When a task is relatively easy, such as deciding whether two items look physically identical (e.g., 2 and 2), processing is faster on within-hemisphere trials. Yet when the task is more complicated, such as determining whether the sum of two numbers equals 10 or more (e.g., 2 and 8), an across-hemisphere advantage is observed (e.g., Banich and Belger, [1990](#); Belger and Banich, [1992](#), [1998](#)). This advantage of interhemispheric communication is especially evident in populations in which the capacity of a single hemisphere is reduced, such as in elderly adults or young children (Banich et al., [2000](#); Reuter-Lorenz et al., [1999](#)). Conversely, in diseases that affect the integrity of the corpus callosum, such as multiple sclerosis or phenylketonuria, the poor ability of the hemispheres to coordinate processing may account for attentional difficulties (Banich, [2003](#)).

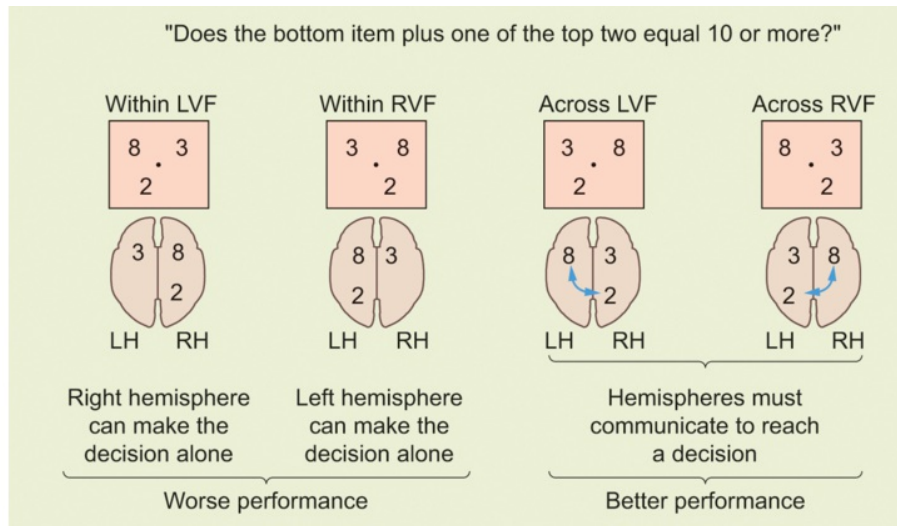


Figure 2.18 Example of interhemispheric interaction aiding in the performance of demanding tasks.

In a task of interhemispheric interaction, two types of trials are compared. In within-hemisphere trials, the critical pieces of information are directed initially to only one hemisphere and the correct decision can be reached without interhemispheric interaction. In across-hemisphere trials, each hemisphere receives only one of the critical pieces of information, so the hemispheres must communicate with one another for the task to be performed correctly. Performance is better on within-hemisphere trials compared to across-hemisphere trials when the task is easy, such as indicating whether two digits are identical. However, performance is better on across-hemisphere trials when the task is harder, such as making a decision about whether the sum of the bottom and either of the top two numbers is equal to or greater than 10. These findings indicate that interhemispheric interaction helps in the performance of more demanding tasks.

Why is within-hemisphere processing faster and more efficient for easy tasks, but across-hemisphere processing superior for difficult ones? As a simple analogy, assume that you are taking a twentieth-century history class and your professor tells you to do your assignments in teams. If your task is easy, such as writing a one-paragraph summary of the major events of World War II, it will probably take you less time to just sit down and write it yourself, rather than having to communicate with a friend and work

on the paragraph together. But suppose you have the more difficult task of writing a 40-page term paper on the same topic. The time and effort required for coordinating with your friend will be small relative to the time you will save by having your friend research and write half the paper. Likewise, as tasks get harder, the brain seems to work better when both hemispheres contribute (see Banich and Brown, [2000](#), for a more detailed discussion of this model).

As we will learn, this bilateral distribution of processing is observed in many modern-day brain imaging studies. For example, a more bilateral pattern of brain activation is consistently observed in the elderly, who are thought to have reduced processing power compared to younger adults (Dennis and Cabeza, [2008](#)). When such a distribution of processing is hindered due to degradation to the structural integrity of the corpus callosum, reductions in cognitive performance are observed (Davis et al., [2012](#)). Yet, such a phenomenon is not limited to the elderly, but has also been observed in younger individuals when they are confronted with particularly demanding tasks (Höller-Wallscheid et al., [2017](#)). This work illustrates a point that we will emphasize throughout this textbook. Unified brain function depends not only on the integrity of specific brain regions performing specific processing, but also the communication between them.

The 1980s and 90s: The Advent of Brain Imaging

The 1980s saw the beginning of a revolution in brain sciences. Whereas previously researchers had to depend on very gross indications of lesion location, such as X-rays of skull damage from entry and exit wounds of projectiles and missiles that had affected the brain (refer back to [Figure 2.2](#)), new methods appeared that allowed researchers to learn more about the anatomy and function of the brain.

Anatomical Methods: Computerized Axial Tomography

In the 1970s, a new breakthrough method for linking brain and behavior arrived on the scene: [computerized axial tomography](#) (CAT, also sometimes called CT). This method is a derivative of X-rays. As you know, X-rays provide a “slice” thorough the body showing, for example, the lungs. CAT scans, however, provide a series of stacked “slices” of the brain (usually between 9 and 12), stacked one above the other, providing insight into a much greater picture of brain anatomy. Like X-rays, the picture provides information on the density of brain structures. Cerebrospinal fluid (CSF) is less dense than brain tissue, which is less dense than blood, which is less dense than bone. In a CAT scan, dense tissue such as bone appears white, whereas material with the least density, such as CSF, appears black. In CAT scans, regions of the brain that were damaged long ago appear darker than the surrounding tissue because they are filled with less dense CSF (see [Figure 2.19](#)). In contrast, areas in which a hemorrhage has recently occurred appear lighter, because blood is denser than brain tissue (see [Figure 2.19](#)).

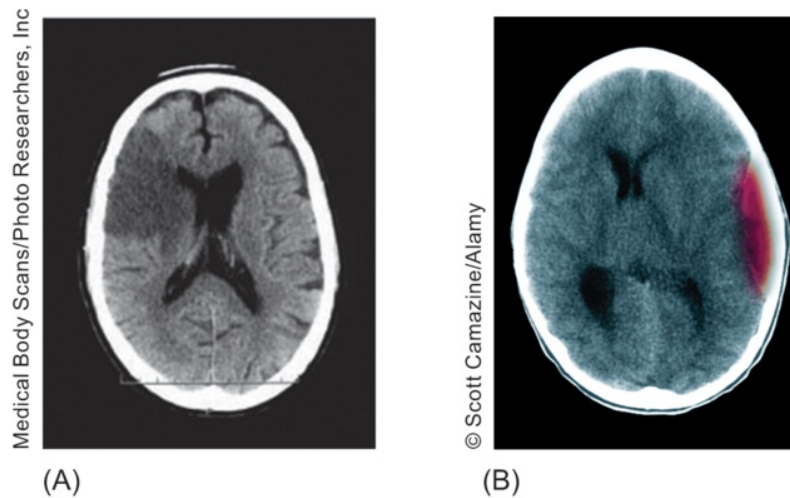


Figure 2.19 Slices of a computerized axial tomography (CAT) scan.

(A) Low-density regions appear dark on a CAT scan. Here the dark region in the frontal lobe of the left hemisphere indicates the site of damage as a result of stroke. Because brain tissue in this region was lost, it filled with cerebrospinal fluid, which is less dense than the surrounding brain tissue (courtesy of Medical Body Scans/Photo Researchers, Inc). (B) High-density regions appear bright on a CAT scan. Here a collection of blood (known as a hematoma) appears as an area of increased brightness in the right temporal lobe, as blood is more dense than brain tissue. Notice that the presence of the hematoma causes a displacement of the lateral ventricle on that side of the brain.

(courtesy of Scott Camazine/Alamy)

Using this method allowed researchers for the first time to create a comprehensive atlas of the human brain anatomy from a method other than anatomical dissection (Damasio, [1995](#)). Importantly, it provided the ability to co-register data from any given patient to such a template, so that damage to a given area across individuals could be linked to similarities in behavioral deficits (Damasio and Damasio, [1989](#)) (see [Figure 2.20](#)). As a result, this era yielded a much improved and refined understanding of what pieces of brain tissue are critical in causing any particular neurological syndrome.

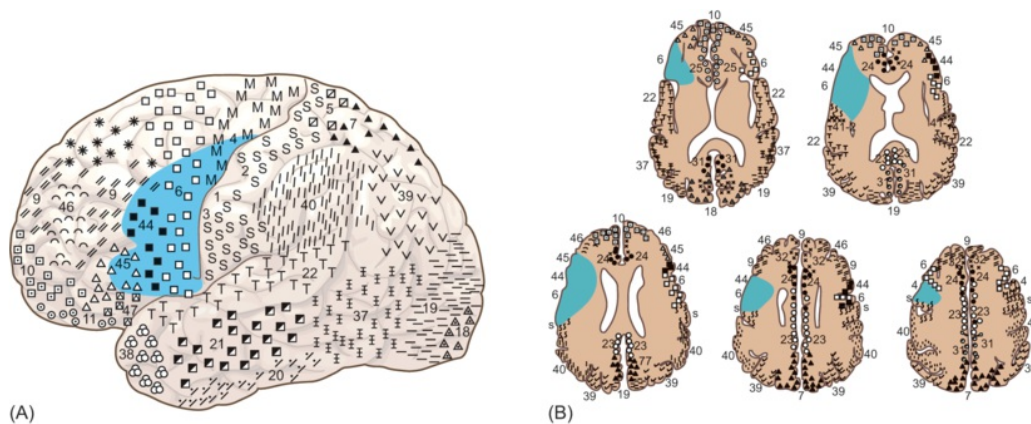


Figure 2.20 Lesion mapping with CT.

In this method, the lesion in a given patient is mapped onto a standardized brain template, which shows the different Brodmann areas as denoted by numbers and geometric symbols. Shown here is the location of the lesion in one patient with Broca's aphasia, as viewed (A) laterally and (B) in oblique brain slices that go from the lowest region of the brain that is affected (top row, left-hand slice) to the highest region (bottom row, right-hand slice). The damage in this patient involves not only Broca's area proper (Brodmann areas 44 and 45), but also other areas that are often damaged, such as the motor and premotor areas (areas 4 and 6).

Functional Methods: Positron Emission Tomography

At the same time, new methods were emerging that allowed researchers to examine brain function. These methods could provide information not only about the brains of individuals who had a neurological disorder, but more importantly about the brains of neurologically normal individuals. It was as if the veil had finally been lifted and the working of the normal brain revealed. No longer did researchers have to rely on the reverse inference of what a brain region was doing by observing what abilities were lost after brain damage. Rather, researchers, could examine, for example, whether Broca's area became more active during speech output rather than inferring its role from the lack of speech after damage to that area.

The most prominent method used during this time period is [positron emission tomography \(PET\)](#). Similar to CAT, PET relies on the use of high-energy ionizing

radiation, although in this case the radiation is emitted by a substance introduced into the body rather than by radiation passing through it. In PET imaging, molecules altered to have a radioactive atom are introduced into the blood supply and carried to the brain. These radioactive molecules become stable and nonradioactive by releasing a positively charged particle called a positron. When the positron collides with an electron, two photons of light are produced that travel in exactly opposite directions. Brain areas of high metabolic activity emit many photons of light, whereas those that are less active emit fewer. From the data received by the detectors, computers extrapolate backward to determine the point from which the photons emanated, allowing the activity of various brain regions to be determined. The process of acquiring a PET image is shown in [Figure 2.21](#).

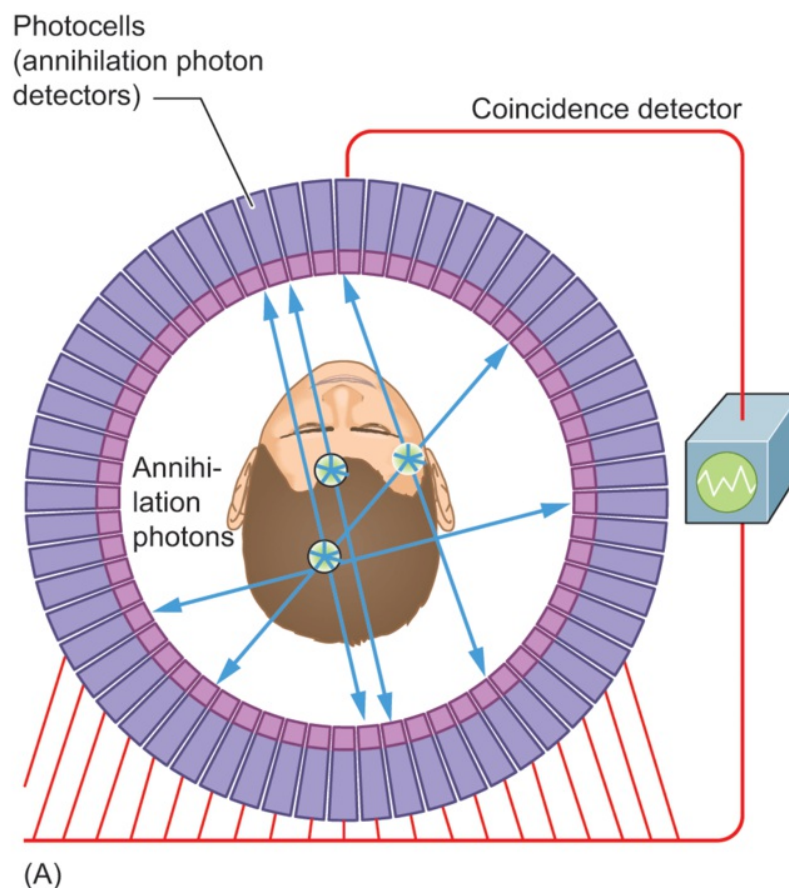


Figure 2.21 An explanation of how positron emission tomography is used to measure brain activity.

A radioactive substance is introduced into the bloodstream and carried to the brain. Typically, this molecule is a radioactive form of a physiologically inert sugar, such as 2-deoxy-2-fluoro-D-glucose with a radioactive fluorine atom (^{18}F) attached, or water containing a radioactive isotope of oxygen (H_2^{15}O). These substances become nonradioactive by emitting a positively charged ion, known as a positron. As the positron travels from the molecule, it collides with an electron, which has a negative charge of the same value, and they annihilate each other. As first realized by Einstein, the annihilation of matter produces energy – in this case, two photons of light that travel from the site of annihilation exactly 180 degrees opposite each other. The coincidence of arrival of two photons 180 degrees apart is detected by a ring of photocells surrounding an individual's head. Brain regions that are very active give off many photons, whereas those that are less active give off fewer.

By extrapolating backward, researchers can determine the source of the photons.

The first such images provided were quite crude, yet nicely confirmed findings from patients with neurological damage (see [Figure 2.22A](#)). For example, when performing a visual task, activation was observed over occipital regions, whereas during an auditory task, activity was observed over the temporal lobes. One of the limitations of PET is that the time required to obtain a picture of the brain's functioning is linked to how quickly a given isotope goes from a radioactive state to a nonradioactive state (known as its half-life), because a significant number of photons must be detected to create an image. In the original studies, a radioactive inert fluorine tag was added to glucose (i.e., sugar) to create 2- ^{18}F fluoro-2-deoxy-D-glucose, often referred to as FDG. This compound was introduced into the bloodstream (Greenberg et al., [1981](#)). As the brain utilized the glucose to aid in metabolism, the fluorine tag became embedded in regions with a high level of metabolism. Because the half-life of radioactive fluorine is about 110 minutes, a mental process had to be performed continuously over a significant amount of time, such as 10 minutes, to enable enough degradation of the radioactive material so it could be recorded and a picture of brain activation obtained. In fact, in

some of the initial studies in the United States, the FDG was manufactured at the Brookhaven Laboratories in Upton, New York on Long Island and then flown to the University of Pennsylvania in Philadelphia, about a 45-minute plane flight! With time researchers switched to a different molecule, ^{15}O , which is radioactive oxygen, that was coupled with hydrogen and infused into the bloodstream. This molecule has a much shorter half-life of about two minutes. As such, not as much time was needed to obtain a picture, now averaged over about 40 seconds, and the resolution was much improved (see [Figure 2.22B](#)).

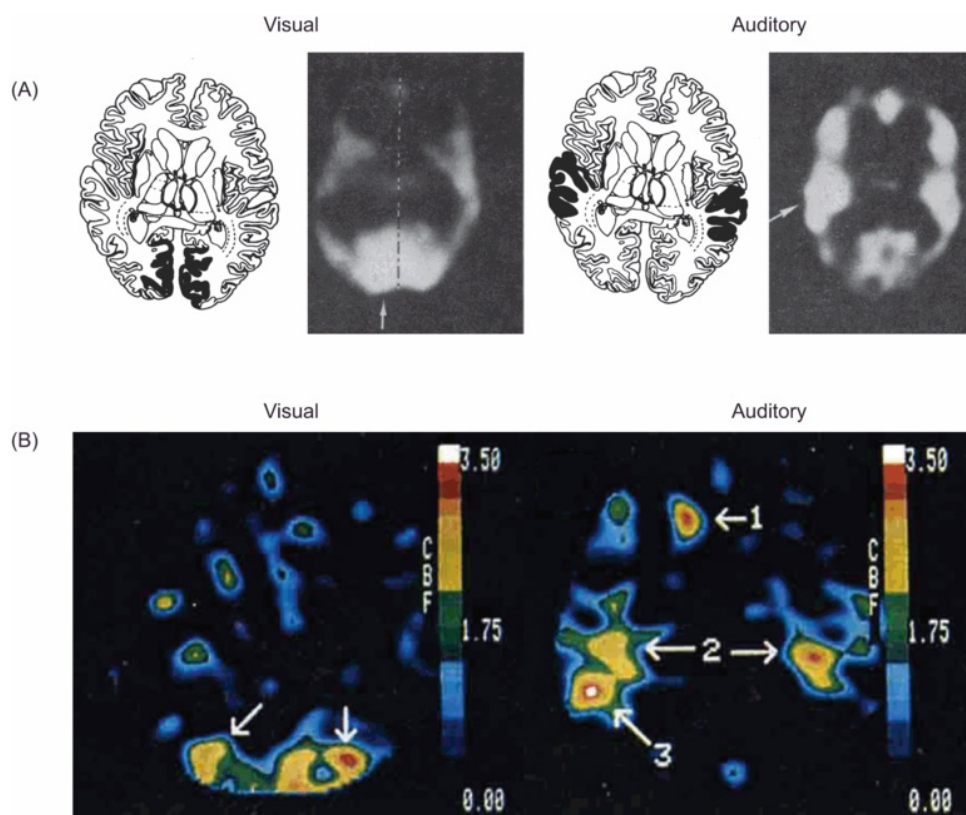


Figure 2.22 Examples of PET scans of the brain when individuals under two different conditions: when they are processing visual information and when they are processing auditory information.

(A) Examples of the poor spatial resolution of the first generation PET scans using FDG. (B) Examples of the later PET scans using radioactive water that had both better temporal and spatial resolution.

(from Petersen et al., [1988](#), 587)

However, this required the researchers to continually infuse water with this radioactive oxygen into a person's bloodstream. Since the half-life of the molecule was so short, the PET center had to be sitting immediately adjacent to a cyclotron, which is required to make an isotope.

Armed with this new tool, researchers used this technique to maximum advantage to investigate the neural bases of a number of different domains, ranging from language to visual attention to musical processing (for a readable account of some of this ground-breaking work, see Posner and Raichle, [1994](#)). Moreover, it started to reveal how the brain systems engaged in mental tasks might be altered, for example, by practice (Raichle et al., [1994](#)).

PET has two main advantages. First, it allows researchers to examine how the brain uses specific molecules (provided that a radioactive [i.e., positron-emitting] version of the molecule can be created). PET has been used in this manner quite successfully in studies of psychiatric disorders to examine the distribution of neurotransmitter binding (see Gatley et al., [2005](#)). If we are interested in the distribution of a neurotransmitter, such as dopamine, we can introduce a radioactively tagged substance that binds to receptor sites (e.g., Wong et al., [1986](#)). This technique has shown, for example, that medicines that reduce hallucinations and delusions in individuals with schizophrenia work specifically by binding to the dopaminergic D₂ and D₃ receptors (see Chapter 1, page [22](#)) for a discussion of different types of dopaminergic receptors) (Stone et al., [2009](#)).

A second advantage of PET is that it provides information on absolute levels of brain metabolism. Increased neural activity is associated with local changes in blood flow, oxygen use, and glucose metabolism (e.g., Sandman et al., [1984](#)), all of which can be measured with PET. Because PET can provide an absolute measure of regional cerebral blood flow (rCBF), rCBF can be compared from one person (or population of people) to the next. For example, let's say a scientist is interested in investigating whether smoking causes a significant decrease in oxygen supply to the brain, and whether that effect increases with age. Using PET, the scientist could directly compare

the rCBF in younger versus older individuals as well as smokers versus nonsmokers. Then he or she might go on to investigate whether such changes in rCBF are related to performance on cognitive tasks.

Yet PET has its limitations. First, like CAT, PET involves ionizing radiation; therefore, the number of scans an individual can undergo per year is limited to somewhere between two and five scans. This makes it difficult to do studies that require multiple scans to examine changes over time, such as changes that might accompany recovery from brain damage, training, or rehabilitation regimens. Second, the temporal and spatial resolution of PET is not optimal. The time periods required to obtain a picture of brain activity (which is determined by an isotope's half-life) are typically quite long. For example, 2-[¹⁸F]fluoro-2-deoxy-D-glucose will yield a picture of brain activity averaged over about 40 minutes, and ¹⁵O provides an image of brain activity averaged over close to a minute. While that may not seem long, consider that most people can decide whether or not a string of letters is a word in about three-quarters of a second. An additional drawback is that PET requires an ongoing ability to create a radioactive isotope that can be continually infused into the individual for the duration of the task. Such a procedure requires a machine called a cyclotron, which is expensive and often available only at major medical centers. Although PET has numerous limitations, today it still remains the preferred technique for examining neurotransmitter function in the brain as well as for studies in which the absolute level of brain metabolism must be determined (such as oxygen uptake by the brain).

The Twenty-First Century: The Brain Imaging Revolution

The breakthrough, however, that made cognitive neuroscience as a field explode has its seeds back in the 1970s when Paul Lauterbur at the State University of New York, Stony Brook and Paul Mansfield at the University of Nottingham independently invented [magnetic resonance imaging \(MRI\)](#), an invention for which they shared the Nobel

Prize in Medicine and Physiology in 2003 (Wehrli, [2004](#)). This method built upon magnetic resonance spectroscopy, which had allowed chemists to determine the “signature” of electromagnetic resonance of specific compounds based on the atoms within them (e.g., carbon, oxygen, nitrogen). They determined how to use such signals to look at the composition of materials, including the brain. The anatomical pictures of the brain obtained using magnetic resonance imaging were far superior to those obtained using CAT scans (see [Figure 2.23](#)) and began to allow a greater understanding of how specific aspects of neuroanatomy are related to brain function.

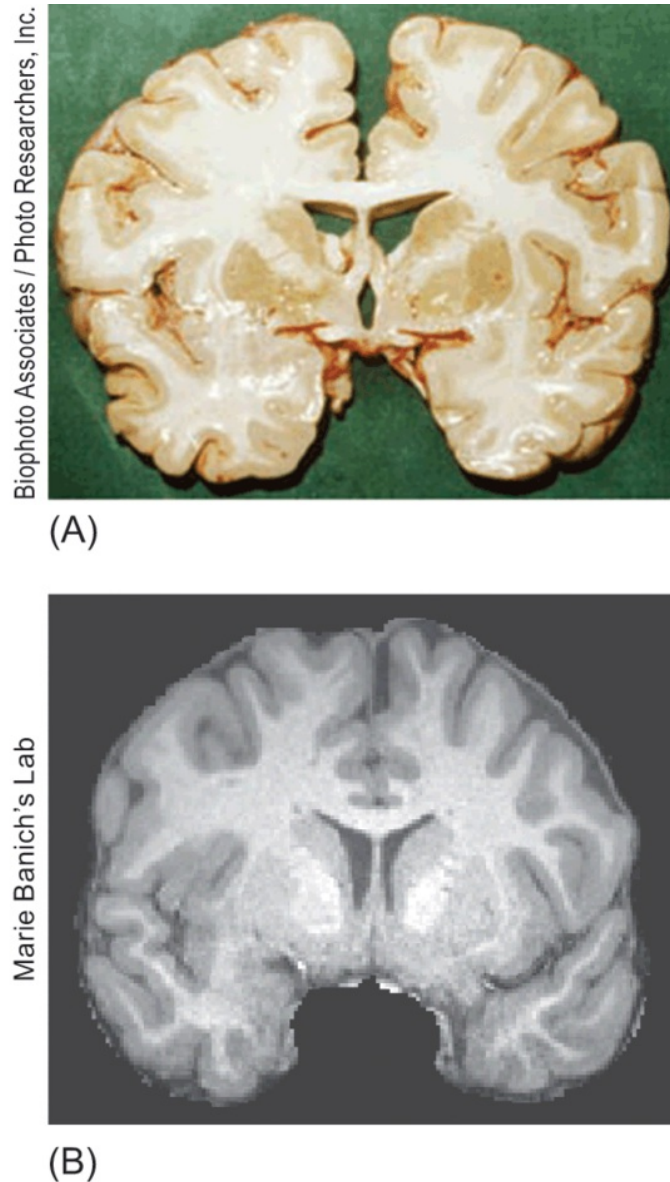


Figure 2.23 A comparison of the clarity obtained in anatomical dissection and magnetic resonance imaging (MRI).

(A) A coronal section through the brain achieved by anatomical dissection. The temporal lobes, Sylvian fissure, putamen, globus pallidus, lateral ventricles, and frontal lobes can be seen (courtesy of Biophoto Associates/Photo Researchers, Inc.). (B) The same coronal slice as imaged by MRI. Note how precisely the MRI reveals anatomical detail.

About a decade later Kwong and colleagues ([1992](#)) determined a way to use magnetic resonance imaging to detect the functional activation of the brain. This method has some very notable advantages over PET scanning. First, it did not involve ionizing

radiation, meaning that individuals could be scanned multiple times. Furthermore, it opened the door to investigations in certain populations, such as children, in whom using ionizing radiation would be questionable for nonclinically related studies. Second, MRI systems were relatively commonplace as compared to PET scanners, and did not need associated equipment, such as cyclotrons. Third, the picture of brain activation that was obtained using these methods typically showed activity averaged over about 2 seconds as compared to about a minute, much more in range with the typical time it takes for most aspects of human cognition.

In the [next chapter](#), we delve in more detail into the ways the multiple of techniques that have been spawned from the use of magnetic resonance imaging are used in cognitive neuroscience. To provide some perspective of how the field accelerated see [Figure 2.24](#), which shows the publication rates of papers using [functional magnetic resonance imaging \(fMRI\)](#) from the late 1990s through the first decade or so of the 2000s, with more papers published using this method between 2010 and 2014 than in all of the previous 17 years combined. While fMRI has become a mainstay in the field, in the [next chapter](#) we discuss the multiplicity of techniques available to cognitive neuroscientists today to enable a more sophisticated understanding of how the brain influences our behavior. However, as clearly shown in [Figure 2.24](#), by the turn of the century, the groundwork had been laid – the brain imaging revolution had begun!

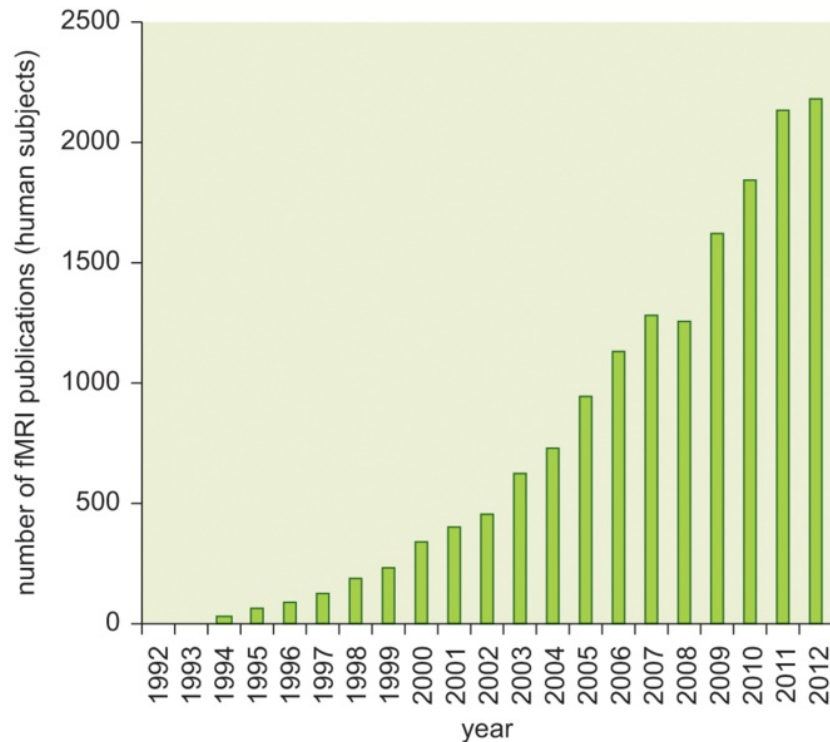


Figure 2.24 The explosion in brain imaging research using functional magnetic resonance imaging (fMRI) that has occurred in the 2000s.

This graph shows the exponential increase in the number of publications per year that use fMRI in cognitive neuroscience studies.

(from Stelzer et al., [2014](#))

Summary

Ancient Times Until the 1800s

- The first person to make a linkage between the brain and behavior was the Roman physician Galen, who noted that gladiators with injuries to the head had trouble thinking whereas those with injuries to other regions of the body did not.
- By showing that a lesion to a specific region of the left hemisphere was associated with difficulty in speech output, Paul Broca introduced the idea of localization of function, that is, that specific brain regions are important for specific mental functions.

The Twentieth Century: Heyday of the Lesion Method

- The lesion method allows scientists to make inferences about what function a brain region performs from observing what behaviors are compromised or absent after damage to that region is sustained.
- Scientists made many important linkages between the brain and behavior in their interactions with many veterans of the two World Wars, especially those who had sustained missile wounds. X-rays showing damaged areas of the skull suggested, by extension, damage to brain regions below.
- Studies using the lesion method employ both a single-case-study approach, as in the case of rare patients, such as H.M., as well as group and multiple-case studies that reveal commonalities across individuals.
- A double dissociation is observed when damage to one brain area, A, impacts one cognitive function, X, but not another, Y, while damage to a different brain area, B, yields the converse pattern: no effect on cognitive function X, but impairs cognitive function Y. When these conditions are met, it is concluded that these two cognitive functions have distinct and separable neural underpinnings.
- While very powerful, the main drawback of the lesion method is that it does not allow us to directly investigate the functions of a particular brain area, as we are only observing how the rest of the brain functions without that area.

The 1960s, 70s, and 80s

- Studies with nonhuman animals, using both the lesion method and recording from cells in the brain, provided complementary and converging information on the organization of the mammalian nervous system and its relationship to behaviors.
- Electrophysiological methods allow recording either directly from the brain itself, or from electrodes on the surface of the scalp.
- Recording from patients prior to excision of brain tissue for the treatment of

epilepsy revealed the organization of the “homunculus” in motor and sensory regions of the brain, as well as helping to delineate brain regions involved in language processing.

- Electrical recordings from the scalp revealed that brain waves vary in their frequency depending on the state of an individual (e.g., degree of alertness) as well as revealing how the processing of information varies over time.
- Behaviors can be disrupted not only by damage to specific brain regions, but also because integration of information between disparate brain regions can be disrupted due to damage to white-matter tracts that connect these regions. These are known as disconnection syndromes.
- The split-brain procedure is an example of a surgically induced disconnection syndrome in which the corpus callosum is severed. This surgery revealed that the corpus callosum is a critical structure for transferring information between the cerebral hemispheres.
- Because the split-brain procedure isolates the hemispheres from one another, studies with human split-brain patients were instrumental in demonstrating that the hemispheres are lateralized for different functions.
- Lateralization of function was also demonstrated through perceptual asymmetries in neurologically normal individuals, and by differing patterns of disability in patients with a unilateral lesion to the left hemisphere as compared to those with a unilateral lesion to the right hemisphere.
- Originally the differences between the hemispheres were characterized as the left hemisphere being specialized for verbal functions and the right hemisphere for spatial functions. Subsequent work suggested that the hemispheres differ in their processing styles: the left hemisphere takes a more piecemeal approach, while the right hemisphere takes a more holistic approach, providing two parallel and complementary means of processing most all information.

- The brain organization of left-handers differs from that of right-handers. On the whole they show less strong lateralization of function, and some show a pattern that is opposite that of right-handers, with language-related abilities lateralized more strongly to the right hemisphere and spatial processing more strongly lateralized to the left hemisphere.
- Transfer of information between the hemispheres via the corpus callosum not only aids in allowing each hemisphere to know what its partner is doing, but such transfer also seems to be a mechanism whereby the processing load can be spread across the hemispheres so as to increase processing capacity under high-load conditions.

The 1980s and 90s: The Advent of Brain Imaging

- Computerized axial tomography (CAT) uses X-rays to provide information about the density of structures, with those most dense, such as the skull, appearing in white, cerebrospinal fluid as dark gray, and brain tissue as light gray. The invention of this method enabled standardized brain atlases, which could be used to co-register damage across patients and link damage in a given area across individuals to similarities in behavioral deficits.
- Positron emission tomography (PET) uses the decay of a radioactive isotope introduced into the brain, typically either glucose or oxygen, to examine brain metabolism. Areas of the brain that are particularly active will take up more of the isotope and provide a greater signal. The use of PET allowed researchers for the first time to record activity from specific brain regions in response to cognitive and emotional demands, thus showing the neurologically normal brain in action.

The Twenty-First Century: The Brain Imaging Revolution

- Magnetic resonance imaging (MRI) provides the ability to examine both brain anatomy and brain function without the use of ionizing radiation, which vastly expanded the questions and populations that could be examined with brain imaging. Moreover, it provided greater anatomical resolution than CAT scans and greater temporal resolution than PET studies, and as such has become a mainstay of cognitive neuroscience research.

Chapter 3

Methods



[Introduction](#)

[Participant Populations](#)

[Clinical Populations](#)

[Neurologically Intact Individuals](#)

[Techniques for Analyzing Behavior](#)

[The Role of Cognitive Theories](#)

[Assessment of Behavior in Brain-Damaged Populations](#)

[Techniques for Assessing Brain Anatomy: Structural Magnetic Resonance Imaging \(sMRI\)](#)

[The Basics of Magnetic Resonance Imaging \(MRI\)](#)

[Regional Brain Structure](#)

[Anatomical Connectivity](#)

[Techniques for Revealing Where in the Brain Activity Is Occurring](#)

[Neurochemical Methods: Positron Emission Tomography and Magnetic Resonance Spectroscopy](#)

[PET](#)

[Magnetic Resonance Spectroscopy](#)

[Oxygen-Related Methods: Functional Magnetic Resonance Imaging \(fMRI\)](#)

[The BOLD \(Blood Oxygen Level Dependent\) Signal](#)

[Task-Based Approaches](#)

- [Resting-State Approaches](#)
- [In Focus: Participating in a Functional Magnetic Resonance Imaging Study](#)
- [Brain Connectivity](#)
- [Electromagnetic Recording Methods](#)
 - [Electroencephalography](#)
 - [Event-Related Potentials](#)
 - [Magnetoencephalography](#)
- [Optical Recording Methods](#)
- [Techniques for Modulating Brain Activity](#)
 - [Transcranial Magnetic Stimulation \(TMS\)](#)
 - [Transcranial Direct Current Stimulation \(tDCS\)](#)
- [Multilevel and Multi-Modal Approaches](#)
- [Combining Computational and Neuroimaging Approaches](#)
- [Summary](#)

Introduction

In this chapter we discuss the different methods that can be used to understand how the brain influences the way we think, feel, and act. Because cognitive neuroscience is an interdisciplinary field of research, it requires integration of information about the brain with information about behavior. Depending on the question under investigation, we may examine different kinds of information about the brain and behavior. We may want to obtain information about the brain at the neuroanatomical, neurochemical, or neurophysiological level.

At a neuroanatomical level, we may need information about the integrity of brain structures, their connections to other brain regions, and their relationship to particular behavioral patterns. For example, knowing that people have specific difficulties in recognizing faces after sustaining trauma to the ventral regions of the right temporal lobe may allow us to infer a connection between that cognitive process and that brain region. We may also require information about the brain at the neurochemical level. For

example, we may want to know how the dysregulation of the neurotransmitter dopamine contributes to the symptoms of schizophrenia. Finally, at the neurophysiological level, we may observe which brain regions are electrically or metabolically active during performance of a specific task. For example, we may want to know the degree to which the right hemisphere is electrically responsive during a musical judgment task.

We can also observe different aspects of behavior. On the one hand, we may want to observe sensory processing in an individual, such as determining whether a person can distinguish high tones from low tones. On the other hand, we may need to examine more central aspects of mental processes, such as the integrity of the memory system. In still other cases, we may want to deconstruct specific mental abilities, such as determining whether a memory deficit is limited to learning new information or extends to retrieving previously learned information as well.

To investigate each of these issues requires particular tools, or research methods. The research methods introduced in this chapter will be referred to throughout this book as we explore the neurocognitive underpinnings of mental activity. During all our discussions, understanding the strengths and limitations of different research methods is important; the adage “You need the right tool for the job” is as apt in cognitive neuroscience as in carpentry. If you have ever tried to use a knife or a dime when you needed a screwdriver, you know that the correct tool can mean the difference between success and failure or between ease and hardship. In cognitive neuroscience, the proper tool may be a particular clinical population, a specific brain imaging technique, or a certain experimental method.

Cognitive neuroscientists must consider how the information they gather in any investigation is influenced by the choice of a particular population and a particular method. Each choice biases the researcher toward observing some aspects of functioning and not others. Consider, as an analogy, that the form of transportation you choose to take from one city to another influences what you see along the way. Taking a plane from one city to another will allow you to clearly see differences in the topography of land, and to distinguish between plains and forest, whereas taking a car

will allow you to see differences in the regional architecture of buildings such as farmhouses and row houses. Given the limitations imposed by any single method of neurocognitive inquiry, you may wonder how scientists can be certain of the conclusions that they draw about brain-behavior relationships. Are scientists as foolhardy as the inhabitants of the Emerald City in *The Wizard of Oz*, who thought the city was emerald because they were wearing green eyeglasses?

As we discuss in more detail later in this chapter, cognitive neuroscientists rely upon a strategy akin to changing your eyeglasses often. In general, researchers aim to gather information on the same question by using a variety of methods with a variety of populations. This technique – examining whether all the answers obtained from a set of interrelated experiments lead to the same conclusion – is known as the [method of converging operations](#). When researchers have examined a question from multiple perspectives and all answers point to the same verdict, the researchers can be relatively confident that they understand a basic aspect of the relationship between the brain and behavior. Let's consider an example of converging operations by examining three representative findings, from different methods, regarding the role played by the parietal lobe in directing attention to particular regions of space. Simultaneously, we'll also consider the potential pitfalls of each method.

Research with monkeys indicates that the response of neurons in the posterior parietal cortex varies depending on the region of space to which the animal is directing its attention (e.g., Lynch et al., [1977](#)). Suggesting that this region plays a leading role in directing attention, such cells appear to synchronize their activity with that of visual areas (Saalmann et al., [2007](#)). Extrapolating from animals, however, may sometimes be problematic because their repertoire of behavior and the organization of their brains may differ from those of humans. Brain imaging in neurologically intact humans reveals an increase in the metabolic activity of the parietal region when a person directs attention to a specific portion of visual space (Corbetta et al., [1993](#)), and such activation varies with how well they exert such attention (Huddleston and DeYoe,

[2008](#)). However, brain imaging techniques usually provide an “average” of activity across a number of individuals, so conclusions about precise anatomical locations can sometimes be difficult to make. Observations from individuals who have sustained a unilateral parietal lobe lesion indicate that the individual ignores the contralateral portion of visual space (e.g., Vallar and Perani, [1986](#)), and subsequent higher-resolution neuroimaging techniques support that association (Mort et al., [2003](#)). However, findings from patients with brain damage are always subject to variability among people, both in the extent of the neurological damage and in the diversity of the people’s experiences before and after the damage.

Although the evidence from any one of these studies alone is not convincing, evidence from all three methods converges on the same conclusion: namely, that the parietal region plays an important role in directing attention to a given region of space. When such convergence occurs, researchers can have more confidence that the answer arrived at is accurate and that the inherent biases of each method are not so great as to obscure their usefulness. Notice that such a converging body of work usually cannot be performed by a single scientist; rather, it depends on a community of scientists with different areas of expertise.

We now turn our discussion to the specific methods used to examine the relationship between the brain and behavior. In this endeavor, we need three critical ingredients. First, we need a population of people on which to test a hypothesis. The group of participants we choose will vary depending on the question we are asking, ranging from children to college students to the aged and from neurologically intact people to those with psychiatric or neurological disorders. Second, we need a way to measure behavior. In some cases, we may want to use specific measures of behavior, and, in other cases, large batteries of tests. Third, we need a means of gathering information about the brain of each person. Depending on the question, we may want information about brain structure, brain function, or both. In the remainder of this chapter, we survey the options available for each of these three critical ingredients and outline the advantages and disadvantages conferred by each choice.

Participant Populations

Clinical Populations

In the [last chapter](#), we discussed the long history in cognitive neuroscience of studies examining behavior in patients with brain damage. Moreover, we noted that such studies have examined not only the location of brain damage but also the severity of damage. We can assume that our inference regarding a particular brain region as important for a given mental function is on more solid ground if we find that the more extensive the damage, the greater is the decrement in performance or alteration of behavior.

A similar logic can be applied to investigations of clinical populations who likely have atypical brain anatomy or function that is not a result of a lesion due to a discrete event (e.g., stroke, gunshot wound). In neuroimaging studies researchers will examine whether the degree of brain activation (or deactivation) shows a significant relationship with a particular characteristic of a clinically relevant group of individuals. For example, a researcher may want to investigate whether increased severity of dependence on alcohol is associated with decreased volume in a particular brain structure, or whether increasing levels of inattention in children with attention-deficit/hyperactivity disorder are associated with reduced activation in specific brain regions during cognitively demanding tasks.

Neurologically Intact Individuals

Although it may seem a bit odd to ponder the thought, neurologically intact people have been a mainstay of the lesion method. They serve as a critical reference population allowing us to determine the degree to which the performance of patients with brain damage is compromised. Clearly, a problem is much more severe if, after brain damage, an individual performs worse than 98% of the people in a neurologically intact reference group than if he or she performs worse than 40% of those people. The larger

the control group assembled for any given test, the more certainty researchers can have in such comparisons.

Well-designed neuropsychological studies must include careful consideration of the characteristics of the individuals composing the neurologically intact control group. The lesion group and the neurologically intact control group must be matched, on a case-by-case basis, as thoroughly as possible with regards to demographic variables such as age, gender, and educational history. In this manner, the study hones in on the degree to which the brain damage, and not other factors, affects performance. When choosing a control group, we may also want to select people who are experiencing stresses similar to those of individuals who recently suffered brain damage. Because people under stress often perform poorly on cognitive tasks, a well-designed study should demonstrate that any cognitive deficit can be attributed to the brain damage and not to the stresses associated with illness, medical treatment, financial concerns, or changes in family dynamics. For this reason, neurologically intact individuals gathered from a different medical population are often good controls because they are under similar stresses but do not have brain damage. One example of such a population is patients who, like those with brain damage, are receiving rehabilitation, but who are receiving such treatment because of bodily injury rather than brain injury.

But of course, research with neurologically intact people may aid our understanding of brain-behavior relations in many important ways besides acting as a control group. Probably most important is that they allow scientists to obtain evidence on how brain structures work together under normal conditions, that is, we get to see the brain in all its glory in everyday action! While this point may seem rather obvious, as we discussed in the [last chapter](#), this has only been possible for a little over two decades.

Parallel to the approach used with clinical populations, variation across people in individual characteristics, such as age, bilingualism, training in music, or IQ, can be used to examine linkages between brain and behavior. Researchers can examine, for example, whether the anatomy of specific brain structures is more influenced by age than others, or whether activation of regions processing perceptual stimuli is influenced

by musical training. Once again, the logic is that if these aspects of brain structure or function vary systematically with such factors, there is likely a relationship between the two.

Techniques for Analyzing Behavior

In order to link brain systems to behavior, we need precise tools to determine and characterize different aspects of behavior. Careful and thoughtful behavioral testing is a critical tool for cognitive neuroscience research.

The Role of Cognitive Theories

Theories of cognitive and emotional function play an important role in both research and clinical practice. Throughout this book, we discuss different theories of mental function. They help to guide investigations into the relationship between the brain and behavior by conceptualizing overarching cognitive functions such as “language” or “spatial ability” as actually consisting of a set of more specific cognitive capacities. To understand the neural underpinnings of functions such as language or spatial ability, we often must break them down into smaller subcomponents, which can then be mapped onto brain function. For example, psycholinguists often describe language as being composed of three parts: phonology, syntax, and semantics. [Phonology](#) refers to the rules governing the sounds of language, [syntax](#) its grammar, and [semantics](#) its meaning. Cognitive neuroscientists can then perform neuroimaging studies that involve giving people some tasks that tap phonology, others that tap syntax, and still others that involve semantics. Scientists can then see whether the brain appears to engage different regions for each of these aspects of language. If so, then it suggests that they are indeed dissociable pieces of our mental make-up.

As another example of why cognitive theories are so important, let’s suppose that a naive cognitive neuroscientist or neuropsychologist does not know or consider psycholinguistic theories of language and encounters a person who cannot correctly

repeat a sentence spoken to her. Our researcher or clinician might conclude, erroneously, that the patient does not “understand” the words in the sentence. However, if this scientist knew from theories of language that the ability to use grammar correctly can be separable from the knowledge of what words mean, the clinician or researcher would test both the patient’s ability to repeat the sentence and also her comprehension – for example, by asking her to point to a picture that depicted what she had just heard. If she could point to the picture depicting the sentence even though she could not repeat the sentence, it would provide evidence that she could indeed understand the meanings of words. At this point, the researcher or clinician could go on to systematically test for difficulties in other aspects of language processing, such as grammar or syntax.

Not only do cognitive theories inform the investigations of cognitive neuroscientists, but investigations in cognitive neuroscience can in turn inform cognitive theories, helping to differentiate those that are plausible from those that are not. For example, as we will discuss in the chapter on language, data from studies in cognitive neuroscience in both healthy and brain-damaged individuals support the conceptualization of syntax and semantics as distinct aspects of language processing.

Because cognitive scientists and cognitive neuroscientists are trying to discover the architecture of the mind, they often devise tasks that allow researchers to test very specific aspects of mental function. These tasks may be quite complicated, in some cases seemingly more like brain-teasers, yet they enable a greater understanding of the neurobiology underlying thought and feeling. Often cognitive neuroscientists will borrow paradigms and approaches used by cognitive psychologists who have carefully considered how different aspects of behavior can be conceptualized and fractionated. However, approaches that work well in the cognitive psychology lab may not be well suited for use in a neuroimaging environment. Nonetheless, the variety, complexity, and duration of tasks that can be used in cognitive neuroscience investigations have expanded greatly from the limited repertoire of tasks that are feasible to do with individuals with brain damage. With this proliferation of possibilities, we have made exponential leaps in our understanding.

Assessment of Behavior in Brain-Damaged Populations

We might assume that the deficits a person has sustained due to brain damage can be ascertained simply by observing behavior, but this is not the case. Think for a moment about the many possible reasons a patient might not be able to provide a name when shown a picture of an animal, such as a zebra. Perhaps the visual attributes of the stimulus cannot be processed because occipital regions were damaged and the person is blind. Or maybe basic visual processing is intact, but the patterns of light and dark cannot be interpreted as the black-and-white stripes of a zebra. Alternatively, maybe the physical form can be perceived (which we know because the patient can correctly choose a horse and not an elephant as looking similar to the zebra) and the patient's memory for zebras is intact (which we know because when asked which African animal is similar to a horse and has stripes, the patient correctly points to the word zebra), but the patient cannot identify that particular form as a zebra. Or perhaps the verbal label cannot be specifically accessed (i.e., if you said "zebra," the patient could point to a picture of one, but if shown a picture of a zebra, he or she couldn't name it). Finally, the patient may have sustained some damage to the vocal musculature that does not allow production of the sound sequence denoted by zebra, even though she or he knows that the picture is that of a zebra. As this example demonstrates, what appears on the surface to be a simple problem may actually stem from numerous complex sources. Often the job of the neuropsychologist or cognitive neuroscientist is to carefully tease apart the possibilities and pinpoint the probable locus of the deficit.

Regardless of whether a brain-damaged individual's abilities are being examined for research or for clinical purposes, a [neuropsychological assessment](#) is generally performed to determine the degree to which damage to the central nervous system may have compromised a person's cognitive, behavioral, and emotional functioning. This assessment is designed to provide a profile of which abilities have been compromised and which ones are intact. Different approaches are used, but typically the assessment

surveys a variety of different abilities, administers some measure of general intelligence, and then does more specific tests in the domain that seems to be most affected, such as language. The definitive reference for neuropsychological assessment, often considered the “bible” for clinical neuropsychologists, is the volume by Muriel Lezak and her co-authors (Lezak et al., [2012](#)), now in its fifth edition.

Most neuropsychological tests were designed for use in the clinic, with the goal of casting a wide net to detect any type of brain dysfunction of either neurological or psychiatric origin. In the past, practitioners would often administer a standardized (also referred to as fixed) [neuropsychological test battery](#), which in a set manner examines a range of abilities from simple tests of sensory function to complex tests of reasoning, from tests of verbal function to tests of spatial function, and from tests of immediate recognition to tests of memory (see [Table 3.1](#)).

Table 3.1 Components of the Halstead–Reitan Neuropsychological Test Battery

| Test | What It Measures | How the Ability Is Measured |
|--------------------------|--------------------------------|--|
| Categories Test | Abstract reasoning | The person views four items on the screen and pushes one of four buttons: different sets of items require different responses (e.g., push the button corresponding to the atypical item, push the button corresponding to the Roman numeral on the screen). The only feedback provided is a bell for correct answers and a buzzer for incorrect responses. |
| Rhythm Test | Auditory perception and timing | The person decides whether two patterns of sounds are similar. |
| Speech Sounds Perception | Verbal abilities | In each trial, the person chooses a previously heard sound from among a |

| | | |
|--------------------------|-----------------------|---|
| Test | Attentional abilities | number of choices. The sounds are nonsense syllables that begin and end with different consonants. |
| Finger Tapping Test | Motor function | The tapping rate of each index finger is determined. |
| Grip Strength Test | Motor function | The strength with which a dynamometer can be squeezed by each hand is assessed. |
| Trail Making Test | Visual search | Part A: The person's ability to draw a line connecting consecutively numbered circles is assessed. |
| | Attention | Part B: The person's ability to connect, in an alternating manner, numbered and lettered circles (e.g., A1B2C3) is examined. |
| Aphasia Screening Test | Language | The person's ability to use and perceive language, to pantomime simple actions, and to reproduce simple geometric forms is assessed. |
| Tactual Performance Test | Tactile memory | Without any visual input (blindfolded or eyes closed), the person must place a set of felt shapes into a single board from which they were cut out. Afterward, with eyes open and the board obscured from view, the person must draw each shape at its correct location on the board. |
| | Spatial localization | |
| Sensory-Perceptual Exam | Sensory loss | The person's perception of simple information in the visual, tactile, and auditory modalities is examined. To |
| | Hemineglect | |

determine whether neglect is present, the investigator presents stimuli to just one side of the body or to both sides simultaneously.

Neuropsychological assessment batteries vary in the perspective from which they set out to determine disability after brain damage. For example, the Halstead-Reitan (Reitan and Wolfson, [1993](#)) was designed over time by Reitan and colleagues as they determined, in an empirical manner, which tests could consistently distinguish between individuals with brain damage and those without. In contrast, the Luria-Nebraska (Golden et al., [1991](#)) had a more conceptual basis, reflecting the philosophy of Alexander Luria, who believed the brain to be composed of three functional and interrelated systems: a brainstem system that is important for overall tone and arousal, an anterior system that is important for the planning and output of behavior, and a posterior system that is important for the reception of information and its processing (Golden, [1981](#)).

The advantages of fixed batteries are that they allow for an “apples-to-apples” comparison of scores of one person to the next, as well as an ability to assess change in a person’s status over time. Nonetheless, they do have some drawbacks, as they assume that one size fits all, which may not be true in less typical cases. Moreover, they provide limited opportunity to customize and further probe areas of suspected deficit.

As a result, there has been a trend in the field toward a more flexible battery approach in which specific neuropsychological tests are administered based on the history, presentation, or complaints of the person being evaluated (Sweet et al., [2011](#)). In general, such a flexible battery approach involves using tasks to assess core competencies, such as memory, visuospatial abilities, language, psychomotor speed and attention, and executive/goal-oriented functions. These tasks are also designed to tap abilities that rely on different regions of the brain. As such, this type of battery provides

a survey of the likely integrity of different brain regions as well as assessing mental abilities (Palta et al., [2016](#)) (see [Table 3.2](#)).

Table 3.2 Principal Cognitive Domains of a Neuropsychologic Assessment and Commonly Used Neurocognitive Tests

| Domain | Brain-related Biologic Relevance | Example Tests* |
|--------------------------------|--|--|
| Memory (working and long-term) | Prefrontal, parietal, cingulate cortex, related thalamic regions, hippocampus, associated medial temporal structures | California Verbal Learning Test; CERAD Word List Learning; WMS-IV Logical Memory; Digit Span Forward |
| Visual-spatial construction | Parietal lobe | Rey-Osterrieth Figure Copy; Benton Visual Retention Test |
| Language | Left-hemisphere language network (Broca and Wernicke areas) | Boston Naming Test; Token Test |
| Attention/psychomotor speed | Dorsolateral prefrontal cortex, posterior parietal, anterior cingulate cortex, subcortical connections | Digit Span Forward; Trail Making Test, Part A |
| Executive functions | Frontal network (dorsolateral, prefrontal, orbitofrontal, posterior parietal, cingulate cortex, basal ganglia) | Digit Span Backward; Trail Making Test, Part B; Stroop Color-Word Test; Clock Drawing |

* WMS, Wechsler Memory Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

This core battery is then likely to be complemented by more specialized and focused tests as the neuropsychologist moves through the examination. Based on performance on these initial tests, the neuropsychologist is likely to make hypotheses as to which deficits best characterize the patient. Each hypothesis is then evaluated with a specific neuropsychological test, and, depending on the individual's performance, the hypothesis is either pursued further by means of another test or abandoned (e.g., Lezak et al., [2012](#)). If it is abandoned, a new hypothesis is generated, and the cycle is repeated until the behavioral deficit is well characterized. The drawback to this approach is that there may be quite some variation in the type of tests that each practitioner uses. Moreover, effectively using this approach depends in part on the skill of the clinical neuropsychologist to ascertain the potential nature of the deficits and to adequately and systematically test for them.

A neuropsychological battery will often contain measures of intelligence. The most widely used measures of intelligence are the Wechsler family of intelligence tests that include the WPPSI-IV (Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition [Wechsler, [2012](#)]), for children aged 2 years 6 months to 7 years 7 months; the WISC-IV (Wechsler Intelligence Scale for Children, Fifth Edition [Wechsler, [2014](#)]), for children aged 6 years to 16 years 11 months; the WNV (Wechsler Nonverbal Scale of Ability [Wechsler and Naglieri, [2006](#)]), to test people aged 4 years 0 months to 21 years 11 months from diverse linguistic backgrounds; and the WAIS-IV (Wechsler Adult Intelligence Scale – Fourth Edition [Wechsler, [2008](#)]) for people aged 16 years 0 months to 90 years 11 months. All of these scales consist of about a dozen subtests. From these scales, one obtains an overall IQ score for an individual as well as subscale scores. For example, in addition to an overall IQ score, the WAIS provides subscale scores for Verbal Comprehension, Working Memory, Perceptual Reasoning, and Processing Speed. The pattern of performance across each of the subtests can provide an important profile of an individual's intellectual strengths and weaknesses.

When deficits are subtle, they may be difficult to detect. Consider the case of a midlevel manager for a small business who, after a car accident, performs about average on the WAIS-IV. How can a clinical neuropsychologist differentiate between the possibility that this person initially had average intelligence and the possibility that brain damage compromised his functioning? To make such a distinction, neuropsychologists and cognitive neuroscientists may use a test to obtain an [estimate of premorbid functioning](#) – that is, a reasonable guess as to how well the person was performing before the injury. The Vocabulary subtest of the WAIS, in which individuals are asked to provide definitions for words, is often used to estimate premorbid IQ. The abilities measured by this subtest seem relatively resistant to brain damage, even that which affects many different arenas of intellectual functioning, such as occurs in Alzheimer's disease. Another test used to estimate premorbid functioning is the National Adult Reading Test (Nelson, [1982](#)), which is an oral reading test consisting of 50 words, most of which are short and irregular in that they do not follow normal rules of pronunciation (e.g., ache). Because the words cannot be sounded out, the ability to read them indicates some previous familiarity with them and therefore provides an estimate of premorbid abilities (Crawford, [1992](#)). When estimates of premorbid intelligence are much higher than present test scores, the results suggest that the brain damage adversely affected the individual's intellectual abilities.

While these tests provide a measure of the level of abilities, neuropsychologists can also make inferences about the nature of deficits by carefully observing the qualitative nature of performance – that is, the strategies an individual uses to perform a task. For example, when a person is asked to copy a complex geometric figure, the neuropsychologist may gain a more precise understanding of the cognitive deficit from viewing how he or she proceeds to do so. If the person starts in one corner of the figure and proceeds to draw each small line as connected to the next, it may suggest that there are difficulties in perceiving overall shape or form.

Although cognitive neuroscientists can be tempted to use neuropsychological tests to examine the range of abilities in neurologically intact populations, there is a hazard in doing so. These tests typically have been designed to detect a lower level of functioning – one that is so far below the average as to indicate brain damage. These tests may be insensitive to variations in abilities across neurologically intact people, who may all perform at a high level regardless of true individual variation in ability. If researchers want an “apples-to-apples” comparison across studies and populations, what is one to do? To address this issue in the United States, for example, the National Institute of Health (NIH) has created the NIH Toolbox (<http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox>), which is a set of neuro-behavioral tasks designed to quickly assess cognitive, emotional, sensory, and motor functions in an automated manner on current-day devices, such as an iPad (see [Table 3.3](#)). It can be used in people aged 3 to 85, and unlike numerous intelligence and neuropsychological tests for which a user must pay royalties with each administration, the NIH toolbox is available free of charge.

Table 3.3 Constructs Assessed Within Each Domain and Subdomain of the NIH Toolbox

| Domain/Subdomain | Functional Constructs |
|--------------------|--|
| Cognition | |
| Executive function | Inhibitory control and cognitive flexibility |
| Episodic memory | Visual episodic memory |
| Language | Vocabulary comprehension, reading decoding |
| Processing speed | Visual processing speed |
| Attention | Visual attention |
| Working memory | Memory for stimuli presented visually and auditorily |

Emotion

| | |
|----------------------|---|
| Negative affect | Sadness, fear, anger; a supplemental apathy measure is also available |
| Positive affect | Positive feeling states, life satisfaction, meaning |
| Social relationships | Social support, companionship, social distress, positive social development; a supplemental measure of social network integration is also available |
| Stress and coping | Perceived stress, self-efficacy, coping strategies |

Motor

| | |
|------------|--|
| Endurance | Cardiopulmonary function, biomechanical and neuromuscular function at a particular intensity |
| Locomotion | Movement of body from one place to another |
| Strength | Muscle ability to generate force against physical objects |
| Dexterity | Small muscle movements which occur in body parts; the ability to coordinate fingers to manipulate objects quickly and accurately |
| Balance | Orienting the body in space, maintaining upright posture under both static and dynamic conditions, move and walk without falling |

Sensation

| | |
|------------|---|
| Olfaction | Odor identification |
| Vestibular | Vestibular ocular reflex |
| Audition | Words-in-Noise; supplemental measures of hearing thresholds and a hearing handicap inventory are also |

available

| | |
|-----------------|--|
| Vision | Visual acuity; a supplemental vision function health related quality of life measure is also available |
| Taste | The ability to perceive taste in different regions of the oral cavity |
| Somatosensation | Pain intensity and pain interference; measures of texture discrimination and kinesthesia were included in the validation study but were not retained for the final Toolbox |

The NIH Toolbox was created so that the same set of tests could be used across different studies or in multisite studies, such as clinically oriented investigations, to enable better comparison of results. For example, perhaps a researcher finds that she doesn't replicate a previous finding or the results at another site. If she has evaluated the cognitive abilities of her sample using the NIH Toolbox, she can determine if profile and level of ability of the participants in her study were significantly different in their abilities (or demographics) from the original study or the other site.

Unlike a complete neuropsychological assessment, which typically takes a half a day or longer, this battery is designed to be administered in two hours or less (Gershon et al., [2013](#)). Nonetheless, as you can see in [Table 3.3](#), the cognition portion of the NIH Toolbox is designed to cover many of the same foundational abilities as are evaluated in a neuropsychological assessment (Weintraub et al., [2013](#)). As a result, the type of tests used in neurologically normal populations in an experimental setting and those employed in a clinical setting are becoming more parallel, enabling better cross-talk between researchers using these two different populations.

Techniques for Assessing Brain Anatomy: Structural Magnetic Resonance Imaging (sMRI)

As we discussed in the [last chapter](#), our ability to link brain structure and function has been revolutionized since the mid-1970s because of the advent of different brain imaging techniques. The intricacies of some of these brain imaging techniques can take a career to master, so the goal here will not be so much to provide an overview of how these techniques work, but rather to focus on the type of information they provide. We also consider the advantages and disadvantages of each technique. We begin our discussion with the mainstay of the modern brain imaging techniques: magnetic resonance imaging.

The Basics of Magnetic Resonance Imaging (MRI)

[Magnetic resonance imaging \(MRI\)](#) is probably the most powerful tool for researchers in cognitive science today. Its power derives from the fact that it can provide information about brain anatomy, both with regards to white matter and gray matter, as well as information on how the brain functions. In brief, MRI machines create a constant magnetic field. Perturbations in this magnetic field are induced and the response of the atoms in the brain is used to derive maps of brain structure and function. MRI machines are classified by the strength of this constant field. Clinical machines typically are 1.5 Tesla (T), with “high-field” research machines generally being either 3 or 4 T (for a reference point, the magnetic field of the earth is 0.0001 T). MRI machines are commonplace in most hospital and university settings, making them generally easily accessible to researchers.

The main limitation, however, is that not everyone can undergo an MRI scan. Because magnetic fields interfere with electrical fields, people with pacemakers (which generate electrical signals to the heart) cannot undergo MRI. Also, anyone with metal in her or his body that is not connected to hard tissue (e.g., a clip on an artery or a metal shaving in the eye such as might be received from welding) cannot have an MRI taken, because the attraction of the metal to the magnet could cause it to move or dislodge. (Metal embedded in hard tissue, such as the fillings in teeth, is not a problem.)

Regional Brain Structure

As you saw in [Figure 2.23](#), MRI can provide very detailed information about brain anatomy. Researchers use this capability to obtain information about the size and shape of different brain structures. For cortical structures, researchers often look at volume (see [Figure 3.1](#)), determining for example if they differ between groups. For example, researchers can examine whether there are differences in gray-matter volume between adolescents with severe substance and conduct problems and those without (Chumachenko et al., [2015](#)) (see [Figure 3.1](#)). For the cortex, volume can be further subdivided into the thickness of the cortical ribbon that we discussed in the [last chapter](#) (see page [51](#)), as well as the surface area of gray matter. These two measures, surface area and thickness, are thought to be influenced by different developmental processes, and also to be differentially affected by genetics as compared to the environment (Panizzon et al., [2009](#)). As such, they are often examined separately. For subcortical structures, researchers will often examine not only volume but also how shape may differ between groups or be affected by different factors. For example, one such application of this method is shown in [Figure 3.2](#), from a study that examined whether the lifetime use of marijuana among recreational users was related to subcortical shape (Orr et al., [2016](#)).

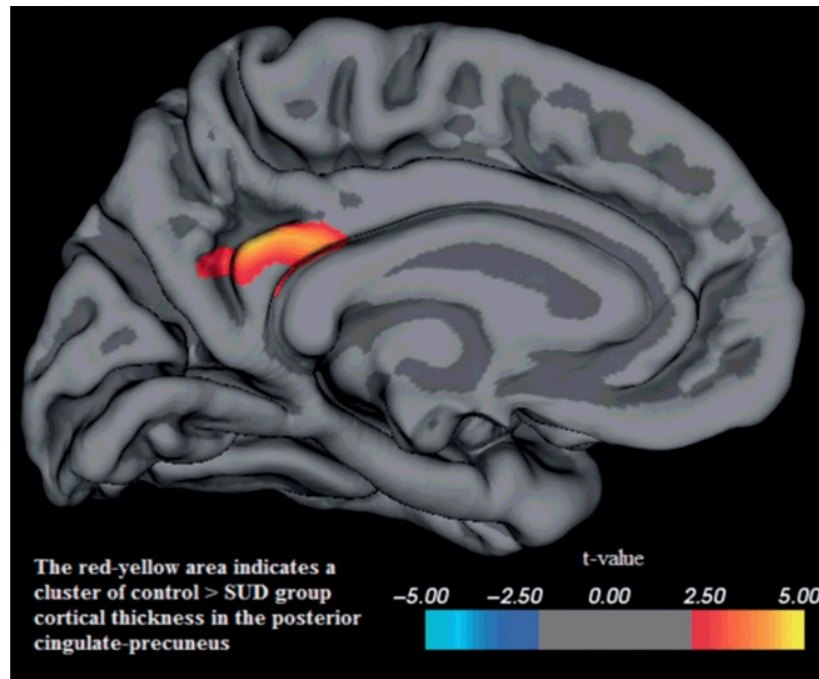


Figure 3.1 An example of group differences in cortical volume.

Shown here in red/yellow are regions of the posterior cingulate cortex and precuneus, portions of the default network for which adolescents with severe substance and conduct problems have reduced cortical volume compared to controls.

(from Chumachenko et al., [2015](#))

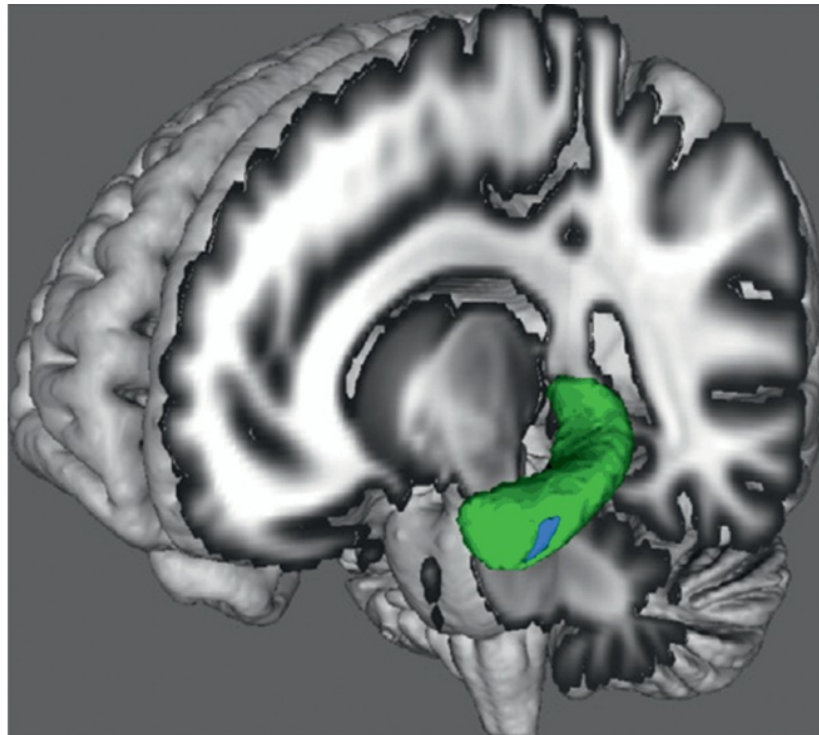


Figure 3.2 Inward deformation of the structure of the hippocampus associated with the amount of lifetime use of marijuana.

Shown here in green is the hippocampus. The area in blue shows increasing inward deformation with increasing number of times that marijuana has been used.

(from Orr et al., [2016](#))

Anatomical Connectivity

Whereas the measures we just discussed generally tell us about gray matter, other methods, such as [diffusion tensor imaging \(DTI\)](#), provide information about white matter. These methods can tell us about the integrity of white matter as well as providing insights into the anatomical connectivity between different brain regions. Briefly, DTI detects the main axis or direction along which water diffuses in nerve fibers. The axis along which water diffusion is greatest indicates the main directional orientation of white-matter tracts, while the degree of diffusion provides information on the structural integrity of those tracts (Mori and Zhang, [2006](#)). [Figure 3.3A](#) illustrates the color mapping key by which the main axis of diffusion is noted, and [Figure 3.3B](#) shows white-matter tracts that have diffusion mainly along the left/right (shown in red),

top/bottom (shown in blue), and front/back (shown in green) axes. For example, the longitudinal fasciculi, shown in green, are large myelinated nerve fiber tracts connecting anterior and posterior brain regions.

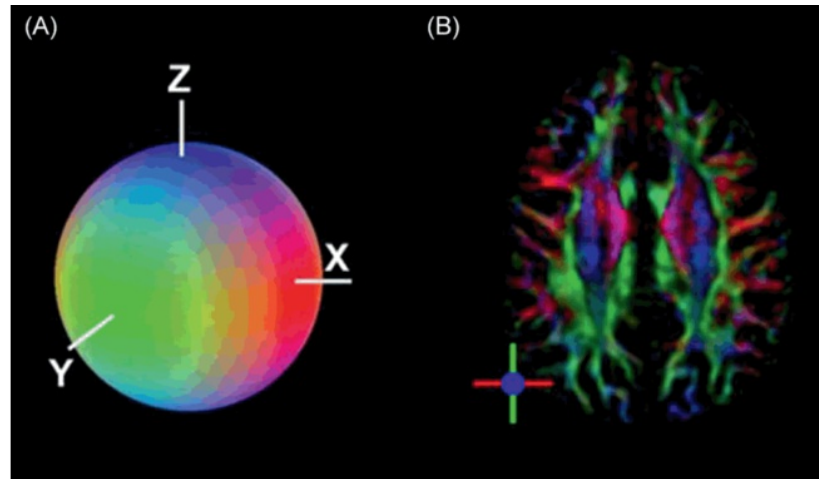


Figure 3.3 Diffusion tensor imaging.

(A) Shown here is the color with which the main axis of water diffusion in a fiber is coded. (B) A horizontal slice of the brain. Fibers going left to right are shown in red, those going top to bottom are shown in blue, and those going front to back are shown in green. Notice the long longitudinal fasciculi, shown in green, that run from the anterior to posterior regions of the brain.

(from Mori and Zhang, [2006](#))

Diffusion tensor imaging is useful for many purposes. For example, it can be used to investigate whether there is less diffusion in particular brain regions as a result of demyelinating disorders such as multiple sclerosis (e.g., Sigal et al., [2012](#)); to examine changes in diffusion during childhood and adolescence (Simmonds et al., [2014](#)); and to detect regions that might indicate a partial or complete disconnection between brain regions (e.g., Vaessen et al., [2016](#)).

By building upon such diffusion tensor information through a method referred to as diffusion [tractography](#), information on probable white-matter tracts can be ascertained. Construction of the probable tracts is based on a number of assumptions, the most basic of which is that regions that are part of the same white-matter tract will have similar

tensor information in adjacent regions (for a review see Ciccarelli et al., [2008](#)). An example of the use of this method to image in greater detail the white-matter tracts that run from anterior to posterior brain regions is shown in [Figure 3.4](#).

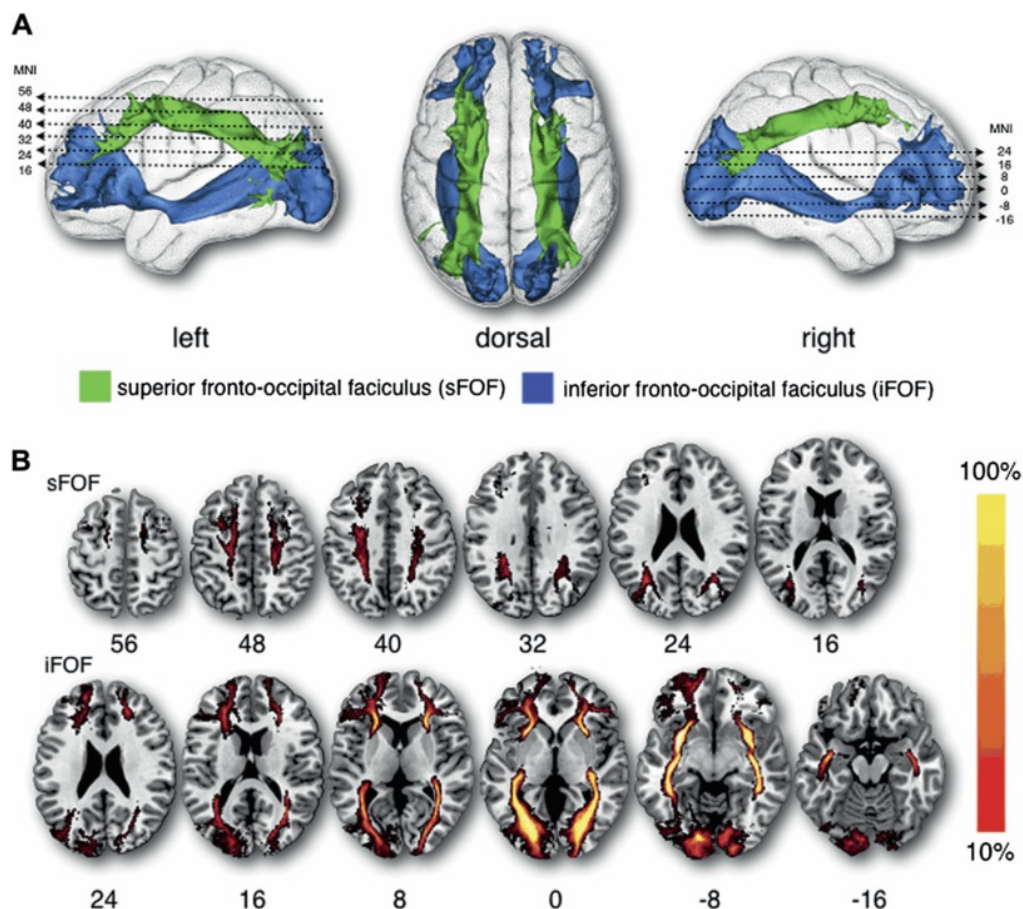


Figure 3.4 An example of DTI tractography.

(A) Shown here is an example of DTI tractography of two major anterior–posterior white matter tracts, the superior fronto-occipital fasciculus (sFOF) (in green) and the inferior fronto-occipital fasciculus (iFOF) (in blue). (B) Shown here are the locations of those tracts as shown in horizontal slices with the sFOF shown in the top row and the iFOF in the bottom row. A brighter color means a higher percentage of participants had a given particular tract localized to this region.

(from Forkel et al., [2014](#))

Techniques for Revealing Where in the Brain Activity Is Occurring

The brain imaging techniques we just discussed provide a picture of the anatomical structure of the brain. However, they cannot tell us about brain function. As an analogy, consider devices that measure the thickness of metal on a car's body as an index of how much a car has been affected by rust. Although these devices provide information about the structural integrity of the car, much the way anatomical brain imaging techniques provide information about the structural integrity of the brain, they cannot tell us how well the car runs. A similar limitation befalls anatomical brain imaging techniques.

For many reasons, cognitive neuroscientists often want to know how well the brain is functioning. But, just as is the case with cars, there are many different ways to evaluate function – by the level of certain critical substances, by the amount of “fuel” consumed, and by the degree of electrical activity. Just as we might want to know the amount of antifreeze in the cooling system of our car, so we might want to measure the concentration of a specific neurotransmitter, such as dopamine, in the brain. Or just as we might want to know how much fuel the car is using, we might want to know how much of the brain's fuel, such as oxygen, is being consumed by different regions. Likewise, while we might want to see whether our car battery is holding a charge, in the case of the brain, we might measure whether aberrant electrical signals are being generated, or we might want to record the sum of the brain's electrical activity.

In this section of the chapter we talk about the first two types of methods, those that measure neurochemical aspects of brain function and those that measure oxygen-related usage, because those provide excellent information about where in the brain activity is occurring. We leave a discussion of electromagnetic methods for a subsequent section, as they are more well suited to providing information on when in time activity is occurring.

Neurochemical Methods: Positron Emission Tomography and Magnetic Resonance Spectroscopy

The methods we discuss in this section provide information about chemical function related to neuronal activity, such as the chemical binding of neurotransmitters to

receptors, the concentration of neurotransmitters, or by-products of neuronal activity. In general, because of technical limitations in gathering information on these compounds, their concentration cannot be localized to a very precise degree within brain tissue. For this reason, these methods are not used as commonly as the fMRI methods that we discuss in the [next section](#).

PET

As you learned in the [last chapter](#), PET works by altering molecules to have a radioactive atom and then introducing them into the blood supply so they can be carried to the brain. Those molecules are then taken up by the brain. As the molecule comes from a nonstable radioactive state to a stable nonradioactive state, two photons of light are emitted that are picked up by detectors around the head.

Today PET is not often used in studies to understand the neural bases of cognitive and emotional function, as it has been superceded by functional MRI. However, there are certain situations in which it provides invaluable information. One of those is with regards to neurotransmitter function, most notably dopamine. For example, raclopride, which has an affinity for D_2 receptors, can be made radioactive with a ^3H or ^{11}C atom. Use of such compounds has been very informative regarding the dopaminergic system, which as we will learn later in the book is associated with reward-related processes, addiction, and executive function. For example, as shown in [Figure 3.5](#), there is less dopaminergic activity in the basal ganglia of a methamphetamine abuser, even after abstinence, than a non-drug user.

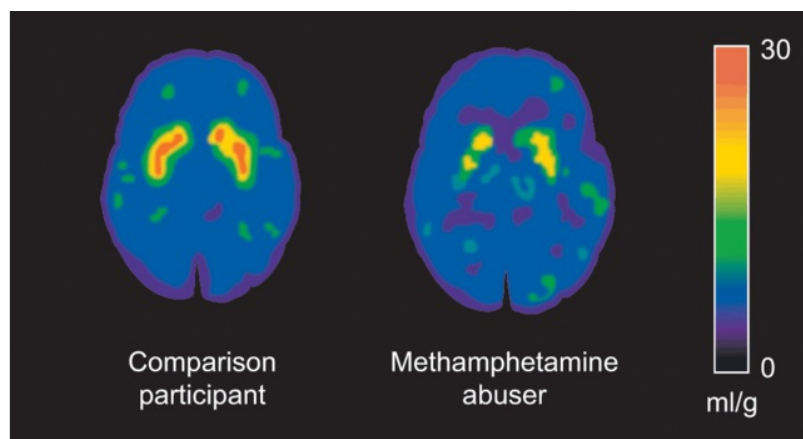


Figure 3.5 Example of a PET image from a study designed to detect dopaminergic activity.

This PET scan comes from a study in which radioactive carbon was attached to a drug that can provide a measure of the activity of dopaminergic cells. Low levels of activity are depicted by blue and green; higher levels of activity are shown by yellow and red. Notice that even after 80 days of detoxification, there is less activity of dopaminergic neurons in the brain of a methamphetamine abuser than in someone who does not use drugs. One of the strengths of PET is that it allows insights into neurotransmitter function in the brain.

A related technique, single photon emission computed tomography (SPECT), is essentially a much scaled-down version of the same technique as PET, using a small set of sensors rather than a ring of sensors. The smaller number of sensors reduces the spatial resolution, or clarity, of the obtained brain image. Moreover, the isotope used with these techniques usually takes longer to decay than the isotopes used with PET; therefore, the picture of the brain activity is less precise because it is averaged over a much longer time interval than with PET.

As a method, PET has two main advantages. First, it allows researchers to examine how the brain uses specific molecules (provided that a radioactive [i.e., positron-emitting] version of the molecule can be created). PET has been used in this manner quite successfully in studies of psychiatric disorders to examine the distribution of neurotransmitter binding (see Gatley et al., [2005](#)). Besides studies of addiction, it has

also shown, for example, that medicines that reduce hallucinations and delusions in individuals with schizophrenia work specifically by binding to the dopaminergic D₂ receptors (see Chapter 1, page [22](#), for a discussion of different types of dopaminergic receptors) (Stone et al., [2009](#)).

A second advantage of PET is that it provides information on absolute levels of brain metabolism. Increased neural activity is associated with local changes in blood flow, oxygen use, and glucose metabolism (e.g., Sandman et al., [1984](#)), all of which can be measured with PET. In fact, PET is considered the gold standard if one wishes to get an absolute measure of regional cerebral blood flow (rCBF) or the cerebral metabolic rate of oxygen consumption (CMRO₂). For example, let's say a scientist is interested in investigating whether smoking causes a significant decrease in oxygen supply to the brain, and whether that effect increases with age. Using PET, the scientist can directly compare CMRO₂ in younger versus older individuals, as well as smokers versus nonsmokers. Then she or he might go on to investigate whether the levels of CMRO₂ are related to performance on cognitive tasks.

Magnetic Resonance Spectroscopy

Because MRI can be tuned to specific atoms, it can be utilized to examine the concentration of some biologically active substances via a method known as [magnetic resonance spectroscopy \(MRS\)](#). These methods are limited, however, in two ways. First, the spatial resolution is not very good, in fact worse than PET. Thus, MRS can provide only very gross information on the location of these substances within the brain (e.g., within a particular portion of the frontal lobe) (see [Figure 3.6](#)). Second, to be detectable by this method, the concentration of the substances must be quite high.

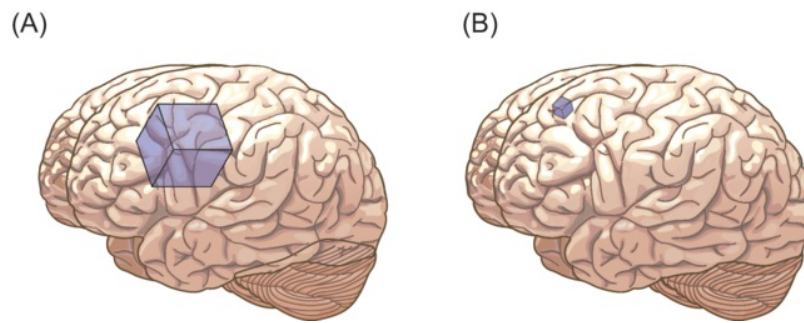


Figure 3.6 Examples of the area of the brain over which information is gathered in magnetic resonance spectroscopy.

Here is an example of the size of a region of brain tissue from which a single MRS measurement can be obtained. (A) The blue cube shows the size of the region of brain tissue from which a single MRS measurement is obtained. As can be seen, the data obtained is over a wide spatial area of cortex (from de la Vega et al., [2014](#)). (B) Shown here for comparison is the size of the region of brain tissue (depicted in blue) from which a single measurement can be obtained with more standard measures of brain function, in this case functional magnetic resonance imaging (fMRI).

Two substances whose concentrations in the brain are high and can be assessed via MRS are glutamate and GABA. As we learned in the [first chapter](#), they are the main excitatory and inhibitory neurotransmitters, respectively. Recent research is examining how their concentration in the brain is linked to mental function (Ende, [2015](#)). In addition, such measurements are also allowing scientists to understand how differences among individuals, both in their personalities and in their cognitive abilities, are related to concentrations of these two neurotransmitters. With regards to personality, for example, people who are higher in anxiety show increased levels of glutamate in the medial prefrontal cortex (Modi et al., [2014](#)). With regards to cognitive abilities, those who have a good ability to guide their behavior by choosing among different alternative options show increased GABA relative to glutamate in the lateral prefrontal cortex (De La Vega et al., [2014](#)).

Another substance that has been examined using this technique is N-acetylaspartate (NAA). This amino acid, found only within the nervous system, has the second highest

concentration of any free amino acid (i.e., one that is not bound to another substance) within the nervous system. Although its exact role in neuronal processes is unknown, a reduction in NAA is thought to index pathological processes acting upon neurons and glia (Martin, [2007](#)). For example, it can be used to index neuronal pathology in disorders such as multiple sclerosis in individuals who have not yet begun to show significant clinical symptoms (Rigotti et al., [2011](#)) or to detect improvements in neuronal function with treatment for Parkinson's disease (Ciurleo et al., [2015](#)). The importance of magnetic resonance spectroscopy may increase in the future if high-field MR systems (i.e., 7 T or higher) become more commonplace. These high-field systems will enhance the ability to detect substances at lower concentrations than is currently available with standard magnets (e.g., 1.5 or 3 T).

Oxygen-Related Methods: Functional Magnetic Resonance Imaging (fMRI)

By far, the technique most commonly used by cognitive neuroscientists is [functional magnetic resonance imaging \(fMRI\)](#), which uses a variation of the anatomical MRI technique just discussed. Here we discuss how this method works and the many types and varieties of data that can be obtained using it.

The BOLD (Blood Oxygen Level Dependent) Signal

Because changes in neuronal activity are accompanied by local changes in other physiological functions, such as cerebral blood flow and blood oxygenation (e.g., Fox et al., [1988](#)), these local changes can be used to infer the activity levels of different brain regions. In the past decade and a half, there has been a veritable explosion of research using a particular fMRI method known as BOLD (Blood Oxygen Level Dependent). This method takes advantage of the fact that oxygenated and deoxygenated blood have different magnetic properties (for discussion of this issue and fMRI methodology, see Bandettini, [2007](#)).

It should not surprise you that blood has magnetic properties if you consider that a lack of iron in the blood causes anemia, which is the reason that many people,

especially women, are encouraged to ensure that their diet contains enough iron. As we learned earlier in this chapter, MRI works by imposing a [static magnetic field](#) and then perturbing it. It turns out that deoxygenated blood makes the static magnetic field inhomogeneous, making it more difficult to detect a signal change. Oxygenated blood does not have such an effect.

When a particular area of the brain is active, the local increase in oxygen-rich blood is greater than the amount of oxygen that can be extracted by the brain tissue. Thus, the relative proportion of oxygenated blood to deoxygenated blood increases in that local region. It is this decrease in deoxygenated blood that allows increased signal clarity from which a picture of brain activity can be derived (e.g., Kwong et al., [1992](#)). For example, when neurons in primary visual cortex fire in response to light, more oxygen is delivered to this region. Researchers can detect the increase in the signal due to decreased presence of deoxygenated blood, compared to the previous state when there was no light, the neurons were less active, and more deoxygenated blood was present.

Notice that fMRI cannot measure a neuronal response directly; rather, it indexes a hemodynamic response, the response of the vascular system to the increased need for oxygen of neurons in a local area. This response is slow, generally starting about 2 seconds after a stimulus is presented, peaking at about 6–8 seconds, and falling back to baseline by about 14–16 seconds. Although this response is drawn out over seconds, we can nonetheless obtain a measure of brain activity on a second-by-second basis (see [Figure 3.7](#)). This temporal resolution is much faster than PET, although it is slow compared to some other methods, such as EEG, that we discuss later in this chapter.

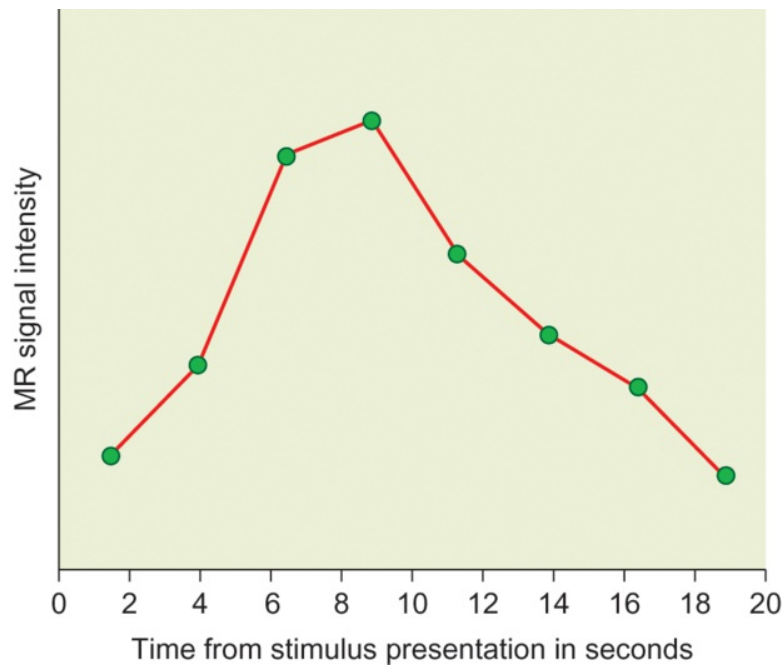


Figure 3.7 Time course of the fMRI signal from the onset of a stimulus.

Notice that there is a lag such that the increase in oxygenation, which is picked up as an increase in MR signal intensity, starts only 2 seconds after the stimulus onset, peaks about 8 seconds later, and then returns to baseline after about 16 seconds.

For a number of reasons, fMRI is a particularly exciting method for making brain-behavior inferences. First, it is a widely available method, as scans can be obtained with clinical MRI machines that have the appropriate hardware to enable the procedure. Second, it is a noninvasive technique, because no high-energy radiation is involved. Third, because of the lack of radiation, multiple scans can be run on a single individual and it can be used with children and women of reproductive age, avoiding the limitations imposed by PET. Multiple scans allow scientists to examine changes in the brain over time, such as those that occur with learning, and allow clinicians to observe changes occurring during the course of recovery or as a result of treatment regimens. A fourth advantage of fMRI is that it provides a measure of brain activity over seconds rather than minutes as is the case with PET. Finally, the precision of scans obtained from fMRI enables us to examine brain-behavior relationships in individuals, which makes fMRI particularly useful for clinical interventions such as neurosurgery (e.g., Matthews et al., [2006](#)).

Task-Based Approaches

The original approach used in fMRI, which still accounts for the majority of studies today, is to examine brain activity in fMRI during the performance of a task. Such studies require a special set-up so that information can be conveyed to the participants and so their responses can be recorded. The typical items of equipment used in a cognitive psychology laboratory cannot be used because they contain metal. Rather all computer and electronic equipment for the study must be located outside the scanner room, in the control room. Special fiber optic or nonferrous metal must be used in all equipment in the scanner room and to link to equipment in the control room. [Figure 3.8](#) shows a typical set-up for a functional neuroimaging study.



Figure 3.8 A typical set-up for magnetic resonance imaging (MRI).

The MR technician (left) and experimenter (right) work in a control room outside of the scanner proper (shown through the window). The MR technician has a console to run the machine and to view images (left). The experimenter has a computer to run the study (right). This computer controls the information that the participant sees while in the magnet, as well as mirroring that information for the researcher. The window allows the technician and experimenter to observe and check on the participant while she or he is in the magnet and a microphone allows communication to ensure that all is proceeding properly.

Generally, because such studies examine the change in the signal from one state to another, the use of task-based fMRI requires that we always compare at least two conditions: one or more conditions of interest, such as “light on,” to a baseline, such as “light off.” In many of the studies discussed later in this book, we will notice that researchers attempt to isolate the brain region involved in a particular function by carefully picking a baseline task against which to measure changes in brain activation associated with the task of interest.

The selection of the baseline task is critical for interpretation of the results. For example, if one wants to determine those regions specifically involved in processing faces above and beyond other objects, then brain activation while viewing faces must be compared to a baseline of brain activation while viewing nonface objects. In contrast, if the researcher wants to determine all the brain regions involved in visually analyzing a face, then brain activation while viewing faces has to be compared to a baseline of brain activation while viewing a very basic visual form such as a cross.

In a standard fMRI study, multiple pictures of brain activation are obtained for each condition of interest and the baseline. Each single acquisition involves getting information on 30–40 slices through the brain, with each slice consisting of 64 by 64 grid of voxels (a voxel is a volumetric pixel), with each voxel being approximately 3 mm³. Thus, in a single acquisition, one is generally obtaining information on brain activation in over 30,000 locations across the brain. To appreciate the amount of data collected in a typical experiment, consider that a single acquisition generally takes between ½ to 2 seconds, and that experiments can run anywhere from 10 minutes to over an hour! Then the signal obtained for all the voxels across the brain for the condition of interest are compared either to another lower-level condition or to a fixation baseline.

Researchers then obtain maps that show which voxels are significantly more activated in one condition than another (see [Figure 3.9](#)). Researchers can also determine whether these patterns of difference vary for two groups (see [Figure 3.9](#) middle), or whether the degree of activation in a given area is related to some demographic (e.g.,

age) or personality (e.g., self-control) ([Figure 3.9](#) right). As you can probably tell, in part our ability to learn so much about the brain has not only been dependent on the advent of MRI machines and the BOLD technique, but also on the increasing sophistication of computer systems that allow for processing of such massive amounts of data.

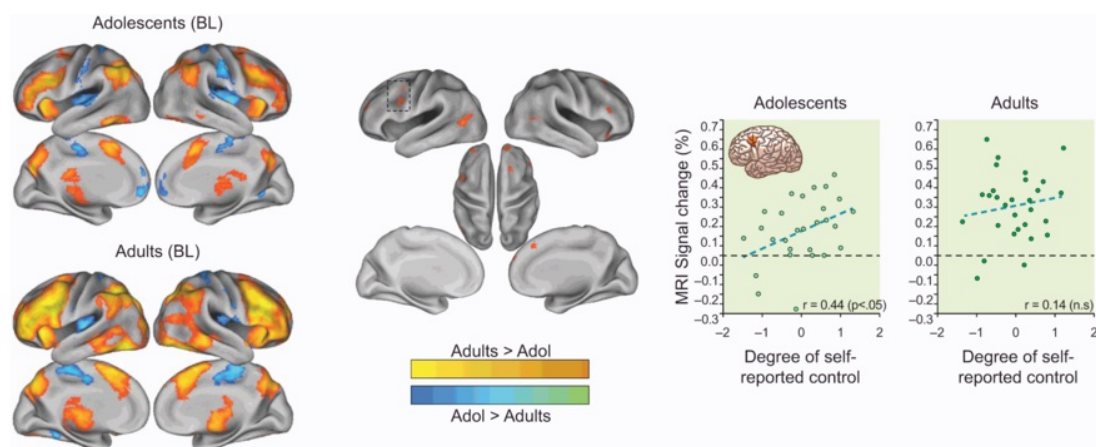


Figure 3.9 Maps of brain activation from an fMRI experiment.

(Left) Shown are two sets of maps, one for adolescent (top) and another for adult participants (bottom). Areas in red/yellow show regions that exhibit greater activation when highly as compared to mildly distracting information must be ignored, whereas areas shown in blue show the opposite pattern (i.e., greater activation during mildly as compared to highly distracting situations). (Middle) Here is the map that compares activation for the two groups, revealing areas that show greater activity in the adults than the adolescents. (Right) Scatter plots of the relationship between activation of the area shown in red and an individual's self-report of their ability to control their behavior in real-life situations both with regards to cognitive (e.g., thinking before acting) and social (e.g., not giving in to peer pressure) domains. Notice that the degree to which adolescents engage this region during highly distracting situations predicts the degree to which they can exert self-control in real life.

(from Andrews-Hanna et al., [2011](#))

Scientists have discovered that it is not just the level of activity that provides information about brain function, but also the pattern of activity. This approach is usually referred to as [multivoxel pattern analysis \(MVPA\)](#). In a series of classic studies (Haxby et al., [2001](#)), scientists found that different classes of objects, such as furniture, tools, animals, and so forth, all activated a common region of visual cortex. In other words, the category of object that a participant was viewing could not be distinguished by the degree of activation. However, if one examined the more fine-grained pattern across the visual cortex, each category of object was associated with a unique pattern of activation.

To understand this concept better, consider the following. Imagine that rather than recording activation information from little cubes of brain tissue, you are determining the usage of electricity from an eight square block region of your town. Just as activation is observed in visual cortex to an approximately equivalent degree regardless of object category, you find that across your eight square block region, the amount of electricity used is similar in summer and winter. In the summer, electricity is used for air conditioning and in the winter it is used for heating and for lighting due to shorter days. However, if you look at the pattern of activation across the houses in your eight square block grid, you notice that it differs during the winter and fall. For example, one set of houses may use relatively more electricity in the summer because those families hate the heat, but less in the winter because they just bundle up with sweaters. In contrast, the pattern of usage is opposite for another set of houses. These houses use less electricity in the summer because they like to spend time outside and don't run the air conditioning, but come the winter they crank up the heat to stay warm. Thus, when averaged across all houses, the overall electricity usage will be equivalent winter and fall, but the pattern of usage will distinguish between the seasons. Likewise, the pattern of brain activation will distinguish the category of items being processed, even though the overall level of brain activation in this brain region will remain similar across object categories because the same process, visual processing, is occurring regardless of object category.

MVPA methods are fascinating because they suggest the possibility of “brain decoding,” that is, that one can infer what someone is thinking about based on the fine-grained pattern of activity within the brain. In this approach, a person is shown a series of different categories of items, such as fruits, tools, furniture, animals, and so forth. Then newer computer classification methods, referred to as machine learning (and which are the types of algorithms used by Google and others) determine the prototypical pattern of brain activity that is associated with one object category (e.g., fruit) and that distinguishes it from other objects categories (furniture, tools, animals), and this is done iteratively for each category compared to all the others.

The net result is a set of classifiers, each of which provides information on the typical pattern of activity that is associated with each category. These classifiers can then predict with a high degree of accuracy which of a series of subsequent items an individual is viewing, by determining which of the prototypical patterns determined by the classifier best matches the current pattern of brain activity (Haxby, [2012](#)). These methods have opened many new and exciting areas of cognitive neuroscience research and are likely to be mainstays for years to come. In the book we cite specific examples, for instance in the study of object recognition (see page [191](#)) and memory (see pages [272](#), [283](#), [291](#)) where these methods have led to important new breakthroughs in our understanding of the relationship between brain and behavior.

Resting-State Approaches

When fMRI was first introduced, most studies involved examining patterns of brain activation while individuals were engaged in some sort of task. Since that time, however, researchers have realized that much interesting information is contained in patterns of activity over time while the brain is simply at rest, such as when individuals lie in the magnet just simply looking at a fixation cross. Examining the time course of activation of the brain at rest has revealed an interesting pattern of co-variation of brain activity across regions. Using statistical techniques researchers have found that there are

“independent” brain networks, and that each network will show similar patterns of increasing and decreasing activation across time, rising and falling together, much like gangs of friends who tend to do things together (Biswal et al., [1995](#)). The way in which these brain regions group together is consistent across people, suggesting that such groupings represent something fundamental about the organization of the human brain.

In Focus: Participating in a Functional Magnetic Resonance Imaging Study

What is it like to participate in fMRI studies of brain function? I have been involved in these studies both as a researcher and as a participant, so I can provide a short description of some of this work from both perspectives. As an experimenter, it is often very helpful to be an initial “pilot” participant before actual data collection starts. It provides a way of checking to make sure that everything is in working order, and also allows you to determine what difficulties might arise during the course of the experiment. This was especially true for me and my colleagues back in 1993 when we first started doing studies using fMRI. It was a relatively new technique then, so before asking anyone else to participate in a study using this new technique, we wanted to see for ourselves what it would be like. That way, we would know exactly what our participants would experience. Because the magnet is quite a different environment than the standard cognitive psychology laboratory, we also wanted insights into the ways in which a “typical” cognitive neuroscience experiment would be transformed by having to perform it in the magnet.

Our first study was very simple; it was designed to determine whether we could detect changes in blood oxygenation over the occipital lobe while a person stared at a checkerboard of red and green squares that reversed color seven times a second. I was one of the first participants. I could not just go and sit in the magnet to be tested. First, I had to carefully look over a checklist to make sure that I did not have characteristics that would preclude a scan. Such

characteristics included having ever had a metal clip placed on any blood vessel during surgery, having a pacemaker, and even having “permanent” eyeliner! Next, I had to check that I had nothing on my person or in my pockets that would be attracted to the magnet or would be influenced by the strong magnetic field – this included belt buckles, jewelry, pens, credit cards, watches, coins, and paper clips, among other things. Such precautions are very important because the strength of the magnetic field in a 1.5 Tesla magnet (the strength of a standard clinical magnet) can pull a pen into the center of the magnet at more than 100 miles per hour, with unfortunate consequences for both pieces of equipment, and this speed is even greater in the now-typical 3 Tesla magnet used for research purposes. Denuded of any metallic objects, I then entered the magnet room. There I was given a pair of earplugs, as MRI scans are very loud. At this point, I was positioned on my back on a table outside the magnet, which is a rather large cylinder, about 8 feet tall by 8 feet wide, with a small hole (known as the bore) in the middle, into which the person is placed (see accompanying figure, which, by the way, is not me).

To obtain good fMRI images, it is very important that the person’s head remain motionless. My colleagues placed pillows around my head to stabilize it before the [receiver coil](#) of the magnet, which is like an enlarged baseball catcher’s mask, was put around my head. Finally, two angled mirrors positioned directly above my eyes were adjusted so that I could view a screen, positioned near my feet, on which the visual stimuli would be projected (nowadays video goggles tend to be used instead for displaying stimuli). Then I was moved into the machine headfirst. My head was placed in the middle of the magnet, which is where the best image can be obtained. Because I’m not tall, I was literally swallowed up into the magnet – my feet were just barely sticking out of the bore.

I found the experience of being moved into the magnet somewhat disconcerting. The bore of the magnet is a small semicircular opening that leaves

little room for even the smallest arm movements and places your nose just inches from the top of the magnet. If you are a spelunker (i.e., a cave explorer), you'd probably feel comfortable, but for people who have any tendency to claustrophobia, the experience can be a bit nerve-racking. I must admit that the first time I was rolled into the magnet, my heart started to race and I felt uncomfortable. But I chatted to my colleagues and forced myself to think about being safely and snugly tucked into bed rather than trapped in a magnet. By keeping my mind on that train of thought, I subsequently found the magnet a comfortable place to relax.

Once the screen at my feet was positioned for optimal viewing, the studies began. MRIs work by setting up a homogeneous static magnetic field around an object. Because a body and a head in the magnet disrupt that field, the machine has to be "shimmed," or adjusted, to take into account the peculiarities of the individual's head and body, and to optimize the signal that the machine will receive. While this was being done, the machine made low, deep "a-clump, a-clump, a-clump" noises, like the sound of a large steel horse slowly loping around a racetrack. After the shimming, an anatomical scan of my brain was taken. The first time I participated in this procedure, my colleagues thoughtfully let me know through an intercom system that the structural scan revealed that I did indeed have a brain!



Box Figure 3.1 To record information about the brain, a head coil is placed around a participant. For studies examining mental function, participants are often asked to respond to stimuli shown on a display screen. To enable the participant to see information displayed on a screen while in the magnet, a prism is positioned on the head coil or a set of goggles is positioned over the participant's eyes (as shown here). A set of response keys are placed on the participant's lap so they can respond to what they are viewing.

Because we were interested in visual processing, the machine was programmed to take a “slice” of my brain's activity that would pass through the calcarine fissure (see figures on the inside front cover of this book), which is where the primary visual areas of the brain are located. During each pair of scans, I first had to close my eyes, a task designed to provide a baseline of the activity level in my occipital cortex when it receives no visual input. Then a checkerboard was flashed to measure the response of my occipital cortex to visual stimulation. This comparison between a baseline condition and a control condition is a hallmark of the design of fMRI studies. The noise made by the machine became different, more tinny and staccato than previously. To round out the day, a high-resolution anatomical scan of my brain with 128 slices was obtained so that a computerized three-dimensional rendering of my entire brain could be constructed. About an hour after we started, my colleagues told me through the intercom that we were done, came into the magnet room, and wheeled me out of the magnet. Although being in the magnet was relaxing, I was glad to get out, stretch my legs, and hear more familiar noises.

While in many ways, an individual's experience within an MRI study today is quite similar, there have been important changes. While our initial studies were performed in a 1.5 Tesla machine that obtained information about brain activity every 2 seconds, a standard machine today has double the field strength (3 Tesla) and can obtain information every $\frac{1}{2}$ second. As such, the resolution of

MRI in both space and time has increased considerably. Another change has been in engineering technologies that created a much larger variety of equipment that can be used in the MR environment. For example, at my current imaging center we have the ability to present visual information on a screen, sound through headphones, small sips of liquid to the mouth through special equipment and tubing, and somatosensory information through MR compatible heat-producing thermodes. We can collect responses from a button-press response box or a voice-recording microphone, track a person's eye movements, record their facial expressions, and collect data on their respiration and heart rate. Compared to a decade or more ago, scientists can probe more sensory modalities, create much more interesting and complex tasks, and record a much larger and richer variety of behaviors while individuals are in the MR environment.

– M.T.B.

In general, the brain seems to divide up into about seven networks of this nature, referred to as resting-state networks. They have been named based on what functions are generally associated with those regions: visual, somatomotor, limbic, default, dorsal attention, ventral attention, and frontoparietal (Yeo et al., [2011](#)) and are shown in [Figure 3.10](#). As an analogy you might think of these different networks as being similar to that pattern of activity across sections of an orchestra: the activity of the horns tends to rise and fall together, but that pattern is distinct from that of the strings, whose activity also tends to rise and fall together, which is in turn separate from that of the woodwinds and so forth.

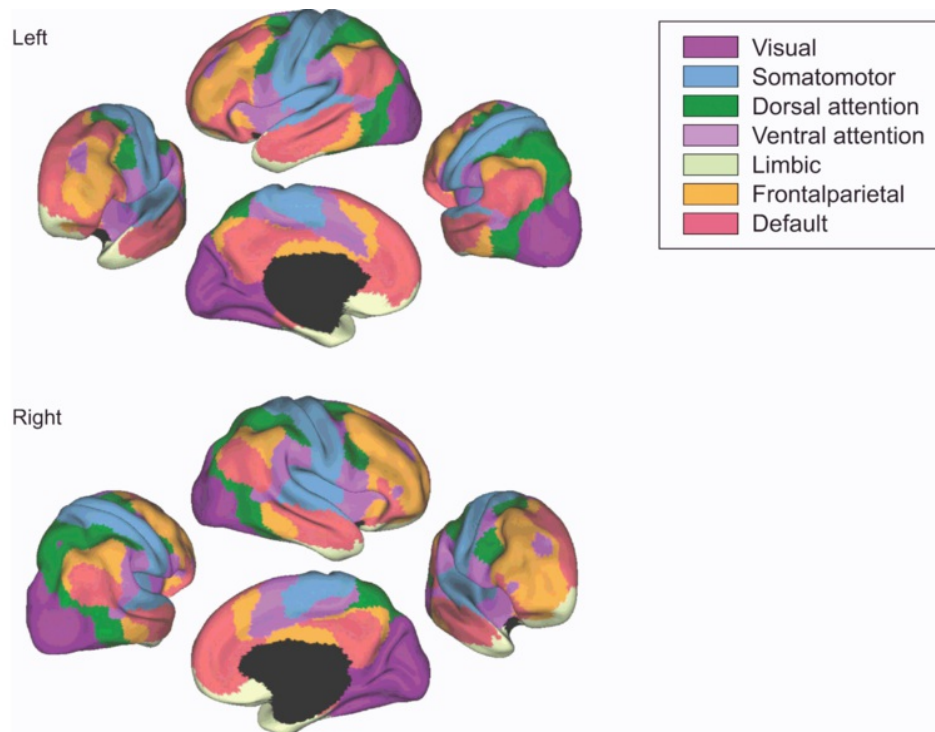


Figure 3.10 Seven major brain networks derived from brain activation at rest.

Activity in each of these networks tends to rise and fall together over time. Names are provided for each based on either neuroanatomical characteristics (e.g., dorsal, ventral, limbic) or the type of process during which they are typically observed to show activity (e.g., attention, somatomotor).

(from Yeo et al., [2011](#))

One can then examine how the composition of these prototypical networks might vary across individuals depending on a specific attribute, such as executive abilities (e.g., Reineberg et al., [2015](#)). Also of interest to researchers is the relationship between activity in these networks. For example, activity in the default network, which is involved in internal mentation, is usually the opposite of that in the dorsal attention network, which aids in directing attention to external stimuli (e.g., Fox et al., [2005](#)). Said differently, when activity in the default network is high, that in the dorsal attention network is low and vice versa (see [Figure 10.12](#), page 318). In a number of populations, such as depressed individuals, this anti-correlation is reduced and may be a marker for disorganization of brain activity (Kaiser et al., [2015](#)).

There has been great interest in resting-state data for a variety of reasons. Generally, the data can be obtained easily and do not require a particular degree of cognitive ability or engagement on the part of the participant. This means they can be used across the lifespan from infants to the elderly. Moreover, only a relatively short neuroimaging session, on the order of 10–15 minutes, is needed to obtain adequate data on any given individual. Furthermore, resting-state data are being used to understand brain dysfunction in psychiatric disorders (e.g., Sheffield and Barch, [2016](#)), being used to aid in neurosurgery (Lang et al., [2014](#)), and to provide insights into lifespan changes from childhood to adulthood (Grayson and Fair, [2017](#)) to old age (Ferreira and Busatto, [2013](#)). It is likely that this method will continue to be leveraged in future neuroimaging studies for its relative simplicity and brevity of administration.

Brain Connectivity

A burgeoning recent development in neuroimaging has been an increased emphasis on understanding more about functional brain connectivity, that is, the interrelationship of activity between different brain regions. We have just discussed one such approach above in which researchers examine which subsets of brain regions group together to cycle up and down together over time. While we just discussed how these patterns can be observed at rest, they can also be examined during performance of a task. And they can be extended to to see whether such patterns differ across groups. For example, researchers have found that when performing a task in which rewards must be delayed, individuals with ADHD showed less of an association in activation between the ventral attention network and the executive control networks (refer back to [Figure 3.10](#)) as compared to controls (von Rhein et al., [2017](#)).

Another approach, if scientists are interested in focusing on a specific discrete brain region, is to use that region as a seed and see whether the activity of other brain regions shows a significant relationship with the seed region either at rest or during task. For example, we might use regions of the prefrontal cortex as seed regions since we know they are involved in modulating activity in more posterior brain regions. In fact,

individuals who show more of a reciprocal relationship between activity in right dorsolateral prefrontal cortex and hippocampus (high prefrontal activity, low hippocampal activity) have a better ability to inhibit retrieval of memories (Depue et al., [2007](#), [2015](#)). When significant relationships are observed, scientists often refer to this phenomenon as **functional connectivity**. While one cannot assume that the seed area is causing activation in the other brain region to go down, measures such as these do provide some evidence that connectivity between brain regions may influence cognitive processes.

Another recent and popular method for examining interaction between brain regions is to look at the interrelationship between brain regions via graph theory, which is sometimes referred to as network analysis (Rubinov and Sporns, [2010](#)). In this approach, the brain is thought to be composed of two hundred or more nodes or regions that can interact with each other, much in the same way that airline routes form a network with airplanes traveling from node to node, in that case from airport to airport. For example, such graph theory metrics suggest that under attentionally demanding conditions, the organization of these networks flexibly reconfigures to allow for more efficient information flow (Spielberg et al., [2015](#)). They can also identify critical hub regions, which can have important implications for behavior. For example, when individuals sustain damage to regions that act as hubs, they tend to show difficulties across a broad array of behaviors and their deficits are relatively severe. In contrast, damage to nonhub regions tends to only affect abilities thought to be localized to that region (e.g., language) without a larger constellation of deficits (Warren et al., [2014](#)). Hence, these methods provide a number of interesting ways to investigate communication between brain regions.

Electromagnetic Recording Methods

The methods we have discussed so far examine the metabolic activity of the brain. In other cases, however, we may want to record the electrical activity of the brain that

results from neuronal firing or the magnetic fields induced by that electrical activity. In animals, we can place electrodes directly into or onto cells and determine what types of stimuli make a cell fire. In humans, we typically record the summed electrical activity of many neurons. Compared with the brain imaging techniques just discussed, electrical measures in humans (including EEG, event-related potentials, and magnetoencephalography) do a relatively poor job of identifying where activity is occurring in the brain. Nevertheless, the electrical methods provide an accurate measure of brain activity on a millisecond-by-millisecond basis, much more rapidly than even the fastest fMRI methods, and thus offer neuroscientists the best available temporal resolution of brain activity.

Electroencephalography

In the [last chapter](#), we discussed how EEG can be used to examine the frequency (periodicity) of brain waves, and how those patterns of brain waves are associated with different psychological states from being drowsy to being alert. In recent years, scientists have been using an approach that builds on this prior work, called time-frequency analysis. In such analyses, activity is examined over time, locked to a specific event. But rather than the summed signal of all activity, the strength of activity in different EEG frequencies is computed. Certain cognitive processes or differences between groups appear to be better characterized by changes in the frequency at which neurons are firing, rather than the absolute level of activity.

To understand this concept better, take a look at [Figure 3.11](#). In this analysis, the raw EEG signal (A) is decomposed into components consisting of various frequencies ranging from the slow frequency 4 Hz (theta) to the mid-range 10 Hz (alpha) to the high-frequency 40 Hz (gamma) (B). For each frequency, a plot of the amplitude of that frequency is determined (C). All such information is combined into a time-frequency plot (D), which shows which frequencies are predominant at a given point in time. For example, in this figure one can see that prior to an event of interest, which occurs at time 0, alpha band predominates but after the stimulus, theta band predominates. Notice that

after the event, there is a suppression of alpha activity, which as we learned earlier, is associated with effortful behavior. Such changes in frequency may occur more predominantly over certain brain regions than others. For example, increases in alpha power are specifically observed over parietal regions when one is trying to inhibit retrieval of a memory (Depue et al., [2013](#)).

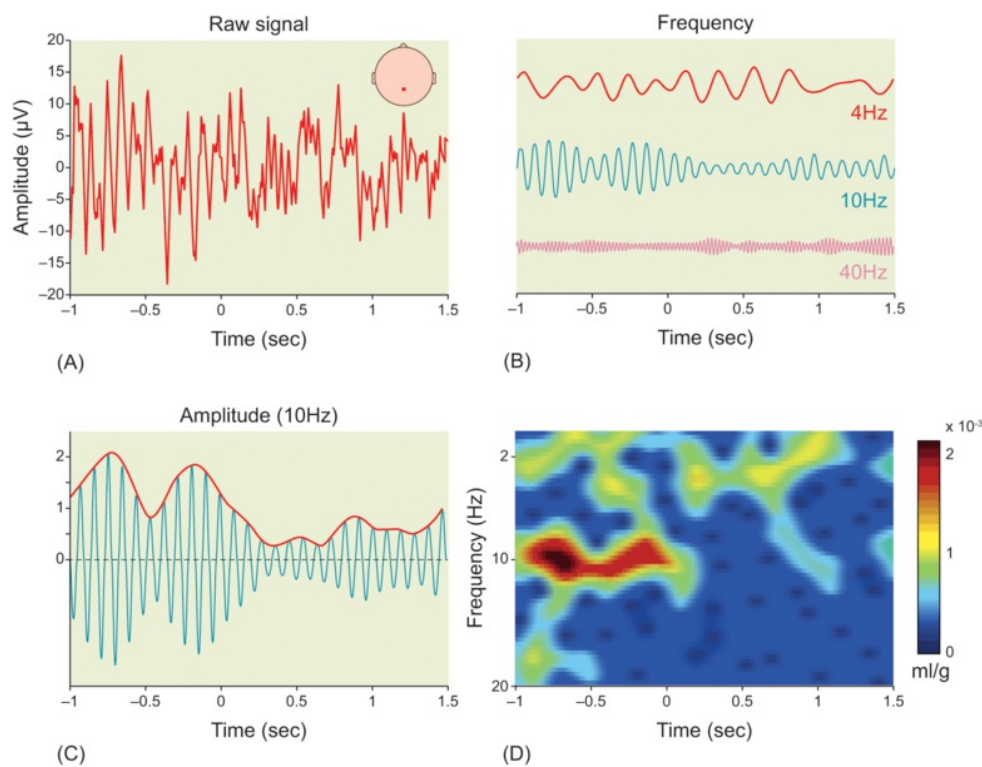


Figure 3.11 Time-frequency analysis of EEG data.

(A) Shown here is the raw EEG signal record over parietal regions (see dot on the figure of the head). (B) This raw signal is decomposed into signals at each of multiple frequency bands. (C) The amplitude over time for a given frequency is calculated. (D) This information is then combined across bands to provide an estimate of which frequency bands predominate at which period of time. Time 0 indicates the event of interest, such as stimulus presentation.

(from Hanslmayr et al., [2011](#))

Another technique used with EEG examines the phase of a particular frequency at any given time point. Because EEG is oscillatory in nature, the activity not only varies

in its amplitude (i.e., the degree of activity), but also its phase. Activity can be at a peak in the cycle (shown in green in [Figure 3.12](#)), at a trough (shown in red in [Figure 3.12](#)), or some place in-between. In the chapter on memory, we will discuss how retrieval of information stored in memory may be affected by which phase of oscillatory behavior the brain is in (Batterink et al., [2016](#)).

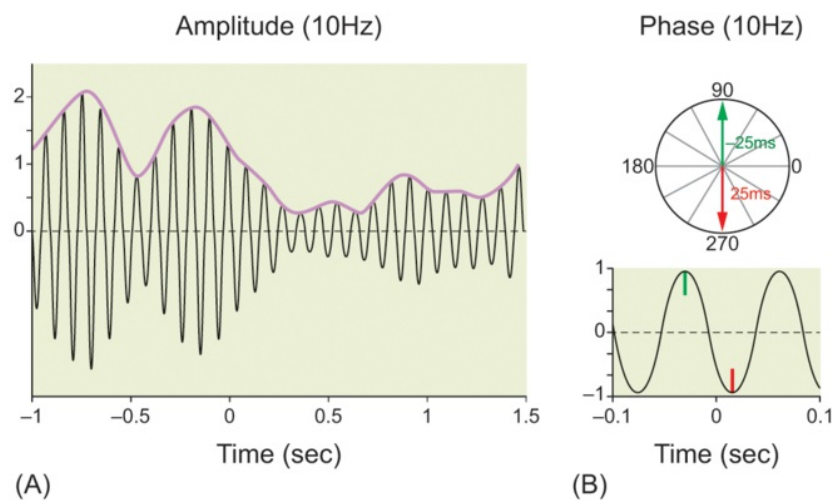


Figure 3.12 Analysis of phase information in EEG recording.

(A) Amplitude provides information on the strength of the signal. (B) Phase in contrast provides information as to whether the oscillatory nature of the signal is at its peak (shown in green), its trough (shown in red), or someplace in between.

(from Hanslmayr et al., [2011](#))

In addition, scientists can examine whether there is a coupling of the peaks and troughs of the activity, referred to as phase coupling, across brain regions or across frequency bands. Such phase coupling can allow for communication and interaction between distant brain regions in the service of mental operations. For example, the coupling of activity in the alpha band in frontal regions with alpha activity in parietal regions increases with the number of items one must hold in mind (i.e., 1 to 6 items) (Palva et al., [2010](#)). The methods of time-frequency analysis and phase coupling are an especially hot topic in cognitive neuroscience these days, especially as they may

provide information on how interactions between brain regions support cognitive and emotional functions (e.g., Roux and Uhlhaus, [2014](#)).

Event-Related Potentials

As we mentioned in the [last chapter](#), whereas EEG recordings provide a continuous measure of brain activity, event-related potentials (ERPs) are recorded in reference to a specific event and are characterized by distinct components (refer back to [Figure 2.8](#)). Components are often divided into two categories: exogenous and endogenous. [Exogenous components](#) are linked to the physical characteristics of a stimulus and usually occur early in the waveform. Because they are evoked by an external stimulus, they are sometimes referred to as evoked potentials. In contrast, [endogenous components](#) appear to be driven by internal cognitive states, independent of stimulus characteristics.

Next, let's discuss the major classes of important components, starting with those that occur earliest in time (refer back to [Figure 2.8](#)). The very early components, occurring within 100 ms of stimulus onset, are linked to sensory processing (Pratt, [2012](#)). This property makes them useful in assessing the integrity of nerve fiber pathways from the sensory receptors to the brain. For example, the points where neurons synapse as information is relayed from the cochlea of the ear to the cortex are, in order, the cochlear nuclei (and superior olive) at the level of the medulla, the inferior colliculus, the medial geniculate nucleus of the thalamus, and then Heschl's gyrus, the primary auditory region of the brain. Information takes time to reach each of these relay points, and when it does, a characteristic component of the waveform is produced. An abnormality in one of these early components implicates a disruption at a specific relay point in the flow of information from the sensory receptors to the cortex.

Components that appear approximately 100 ms after a stimulus is presented include the P100 and N100. At this point, ERPs are no longer driven solely by sensory information, but can also be modulated by attention (see Luck and Kappenman, [2012](#)). The P100 component is a positive deflection observed between 80 and 140 ms post-

presentation, whereas the N100 is a negative deflection observed about 100 ms post-presentation for auditory stimuli and between 160 and 200 ms post-presentation for visual stimuli. Scientists can observe the effect of attention on these components by asking individuals to pay attention to information presented in one location but not another, such as attending to information presented to the right ear but not the left. When an individual's attention is directed to the location at which the stimulus is presented, the size of the P100 and N100 are increased relative to when that same stimulus is presented but the individual's attention is directed elsewhere (Mangun and Hillyard, [1990](#)). Notice that the stimulus in both cases is identical – all that varies is whether the individual is attending to its location.

The N200, a negative deflection at about 200 ms post-presentation, is known as the mismatch negativity (for review see Näätänen and Kreigipuu, [2012](#)). It occurs when an individual is presented with an item that is physically deviant from that of the prevailing context. For example, if someone is listening to a series of tones, most of which are low in pitch, a high-pitched tone will elicit an N200. Unlike the N100, this effect occurs regardless of whether the individual is attending to the location in which the deviant stimulus appears (e.g., Näätänen et al., [1978](#)).

One of the most studied components is the P300, which is a positive deflection found approximately 300 ms post-stimulus (see Polich, [2012](#), for review). Although researchers disagree on exactly what the P300 measures, it appears to be related to attention and the updating of memory, as occurs when a person modifies his or her current model of the environment to include new incoming information (Donchin and Coles, [1988](#)). The P300 occurs in numerous situations; however, the classic situation that elicits a P300 is an experimental procedure called the oddball paradigm. In this paradigm, an individual hears a series of tones at consecutive intervals, most of which are at one pitch (e.g., a “beep”) and a minority of which are at another pitch (e.g., a “boop”). A larger P300 generally occurs to the oddball, the boop, than to the regular items, the beeps. Typically a P300 is observed when the individual must pay attention to

an item, the oddball, and that oddball is distinct from the information currently held in memory (necessitating the updating of memory).

The P300 is distinct in two ways from the mismatch negativity that occurs when a physical deviance is detected. First, a P300 can be elicited by the lack of sensory stimulation, such as silence. If, for example, a person hears a series of tones punctuated periodically by silence when a tone should occur, a P300 is elicited by the silence because memory must now be updated. Furthermore, whereas the mismatch negativity appears to occur relatively automatically, regardless of whether an individual is paying attention to the items, the person must be engaged in processing the stimulus for a P300 to occur. Because of this feature, it has been used as an index of how much attention an individual is devoting to processing a stimulus (e.g., Kramer et al., [1985](#)).

Another late component that has been linked to psychological processing is the N400. This negative-going component appears approximately 400 ms after stimulus presentation and occurs when individuals detect semantic anomalies (see Kutas and Federmeier, [2011](#), for review). So, for example, if your ERP were being recorded at this moment, an N400 would probably be observed as you read the last word of the following sentence: “Running out the door, Patty grabbed her jacket, her baseball glove, her cap, a softball, and a skyscraper.” In contrast, the N400 would be absent if the same sentence ended with the word “bat.” The amplitude of the N400 increases with the deviance of a word relative to the prior context of the sentence. For example, your N400 for the following sentence, “Running out the door, Patty grabbed her jacket, her baseball glove, her cap, a softball, and a lamp,” would be smaller than your N400 for the first sentence, because lamp is less deviant a word than skyscraper (i.e., Patty could actually grab a lamp, but not a skyscraper). However, an N400 would still be elicited by the second sentence because you would expect Patty to grab another piece of softball equipment, not a piece of furniture (e.g., Kutas and Hillyard, [1980](#)).

An even later component, the late positive potential, is influenced by affective factors. This component extends into the range of 600–800 milliseconds post-

stimulation (see [Figure 3.13](#)), and is greater for affectively valenced information (words, faces, pictures), either positive or negative, as compared to neutral stimuli (e.g., Schupp et al., [2000](#)). It should be noted that while we have emphasized the influence of cognitive factors on ERP components, they are influenced by emotional (see Hajcak et al., [2010](#) for review) as well as social factors (see Ibanez et al., [2012](#), for review).

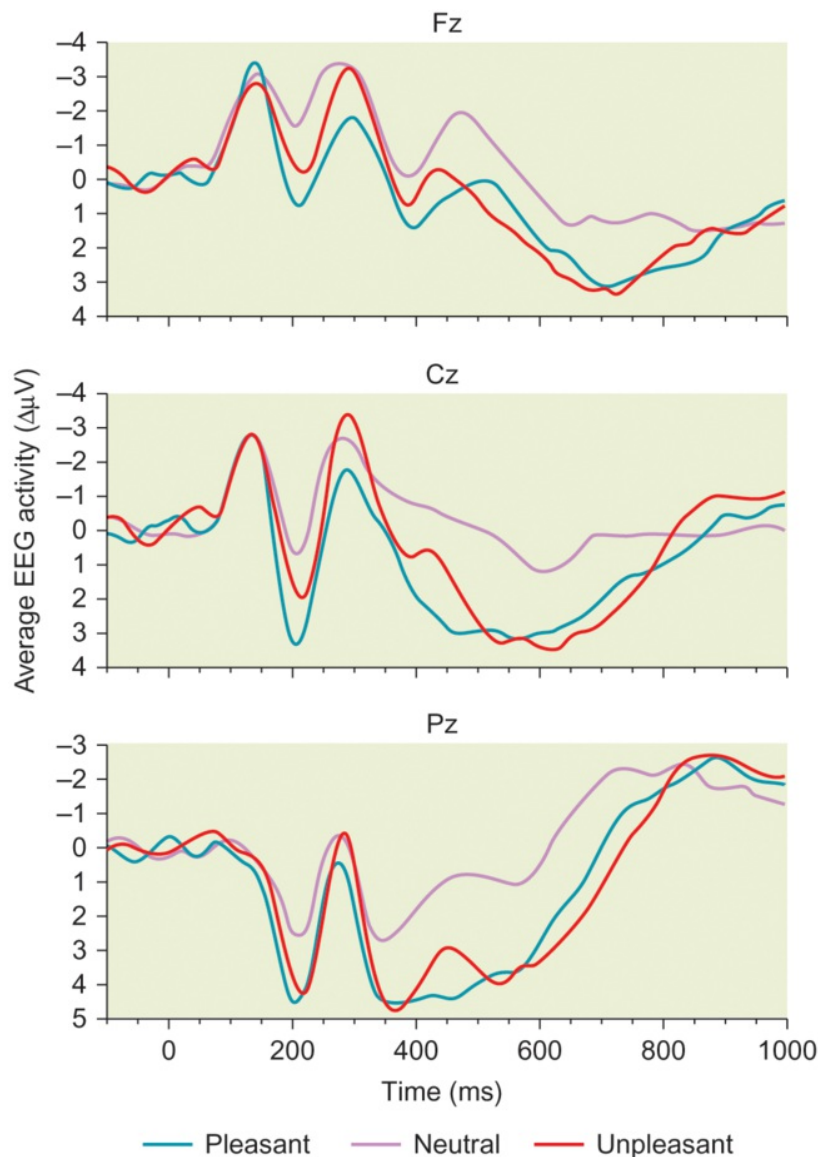


Figure 3.13 Examples of the late positive potential.

This potential is generally observed beyond 400 or so milliseconds post-presentation and is different in amplitude for emotionally valenced information than emotionally neutral information. Notice that there is a greater response over frontal (Fz), central (Cz), and parietal (Pz) leads to information that is either pleasant (shown in blue lines) or unpleasant (shown in red lines) as compared to emotionally neutral information (shown in the purple line). Note that the graph is arranged so that greater positive values appear toward the bottom of the graph (see y axis).

(from Schupp et al., [2000](#))

A review of the components and the psychological processes with which they are associated is presented in [Table 3.4](#). (A more detailed review of ERPs and their relations to psychological processes is presented in Fabiani, Gratton, and Federmeier, 2007).

Table 3.4 Basic Components and Psychological Processes Associated With Event-Related Potential (ERP) Components

| ERP Component | Time Period (ms)* | Eliciting Conditions | Associated Mental Processes |
|----------------------------|-------------------|---|--|
| Sensory components | 0–100 | After the receipt of sensory information | Transmission of sensory information from the periphery to the cortex |
| N100–P100 | 100–300 | When subjects are paying attention to the portion of the stimulus stream in which the material was presented | Selective attention |
| Mismatch negativity (N200) | 200–300 | When a stimulus is physically deviant from other recent stimuli; it is not much affected by whether the individual is paying attention to the portion of the stimulus stream in which the deviant | Detection of physical deviance |

| | | | |
|-------------------------------|---------|---|---|
| | | item is presented | |
| P300 | 300–800 | When individuals must pay attention to the rarer of two events, even if that rare event is the absence of sensory stimulation (e.g., silence) | Memory of context updating |
| N400 | 400–600 | When items deviate in meaning from what is expected | Detection of semantic deviance |
| Late Positive Potential (LPP) | 400+ | When items have an emotional valence as compared to neutral | Detection of affectively valenced information |

* Indicates time post-presentation.

ERPs are extremely useful because they provide some information about the time course with which information is processed in the brain. For example, we have learned that attention acts to enhance processing of task-relevant materials by at least 150 milliseconds post-presentation. Still, ERPs do have some drawbacks. The pattern of brain activity on the scalp cannot tell us with certainty the location of the dipole or dipoles within the brain that are generating such a pattern. Any given pattern of activity on the scalp could mathematically be produced by a variety of generators or sets of generators within the brain, a difficulty known as the inverse problem. For this reason, researchers have focused on utilizing computer models of the head that make certain

simplifying assumptions to help them more precisely localize the neural generator or generators within the brain (e.g., Scherg, 1992). An example of dipole modeling of the source of a component is shown in [Figure 3.14](#). The additional information provided by these high-density recording systems, which often have up to 128 leads, aids in the modeling process (e.g., Potts et al., 1996; see Luck, 2014 for review).

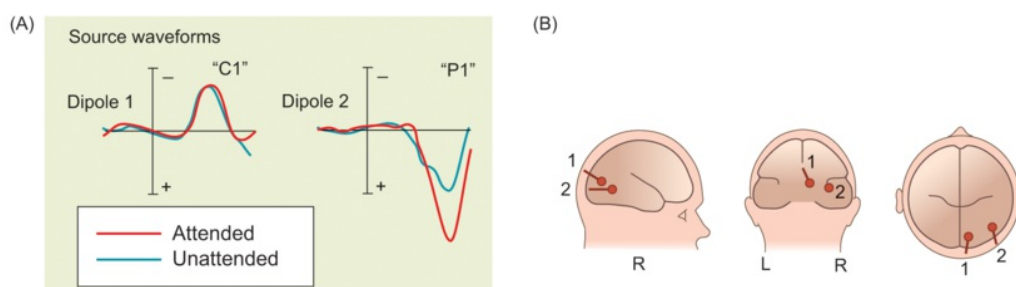


Figure 3.14 Results of a dipole modeling procedure.

In this experiment, individuals were shown a simple visual stimulus (a circular checkerboard) and told to attend to information on the left side of space. (A) Shown here are the responses to attended items, depicted by the red line, and unattended items, depicted by the blue line. Dipole 1 models the source of the C1 waveform. Notice that its amplitude does not vary depending on whether an item is attended or not. Dipole 2 models the source of the P1 waveform, which reflects attentional modulation of sensory processing as indicated by the larger response to attended than unattended information. (B) The location of these two dipoles as seen from a lateral, coronal, and horizontal perspective. The location of Dipole 1 is near the midline of the brain and near the calcarine fissure, consistent with a position within primary visual cortex. Dipole 2, however, is positioned more laterally, consistent with a location in secondary visual processing areas.

Magnetoencephalography

Rather than recording the electrical potentials to index brain activity, a related method, [magnetoencephalography](#), known as MEG, records the magnetic potentials produced by brain activity. Recording magnetic fields has some advantages and disadvantages over recording electrical potentials. Whereas electrical currents produced in the brain

are carried in varying degrees through brain tissue, cerebrospinal fluid, the skull, and the scalp, the strength of magnetic fields is not as influenced by these variations in tissue. Moreover, the strength of magnetic fields falls off from their source in a systematic manner (with the square of the distance), so the strength of the magnetic field recorded on the outside of the head can help provide some information about how deep within the brain the source is located. However, because the size of the magnetic fields produced by the electrical activity in the brain is very small – in the range of 50–500 femtoTeslas (fT), which is 1 billionth the size of the earth’s magnetic field – an MEG device requires a special magnetically shielded room. This room, usually made of aluminum (which is a nonmagnetic metal), shields not only against the earth’s magnetic field but also other electromagnetic radiation, such as microwaves, radiation contained by electrical currents in everyday buildings, and the magnetic field generated by the sun.

Currently, the two most common clinical uses of MEG are (1) to localize the source of epileptic activity and (2) to locate primary sensory cortices so they can be avoided during neurosurgical intervention (e.g., Tovar-Spinoza et al., [2008](#)). MEG is especially helpful in cases where neither EEG nor a brain imaging method such as fMRI or PET can definitely locate the source of epileptic activity or the location of primary sensory cortices. In research, MEG has been used to understand a variety of cognitive processes, including language, object recognition, and spatial processing among others, in neurologically intact individuals (see Baillet, [2017](#), for a discussion of how MEG works and its application to cognitive neuroscience).

Optical Recording Methods

Currently there is one technique that can provide cognitive neuroscientists with the ability to simultaneously obtain information about the source of neural activity as well as its time course. In this method, called [optical imaging](#), a laser source of near-infrared light is positioned on the scalp. Detectors composed of optic fiber bundles are located a few centimeters away from the light source. These detectors sense how the

path of light is altered, either through absorption or scattering, as it traverses brain tissue (see [Figure 3.15](#)).

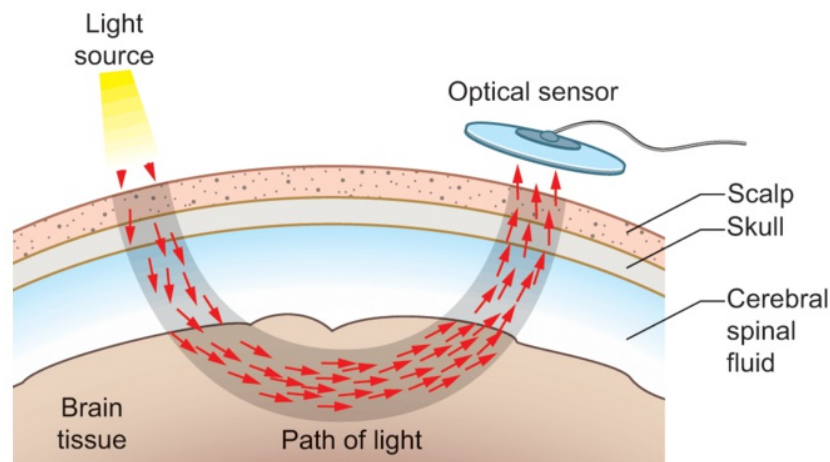


Figure 3.15 The principles of optical imaging.

A light source at the surface of the head emits near-infrared light that travels through the skull into the brain. The light then passes through the brain and emerges at the surface, where it can be detected. The path that the light takes through the brain can vary depending on a number of factors, including the geometry of the head. Hence, the set of possible paths is shown here as a crescent-shaped gray area. The optical signal is analyzed to determine how much light is absorbed, which results in a decrease in intensity, or how much the light is scattered from its ideal path, which causes a delay in its receipt at the sensor.

This method can provide two types of information. First, it can provide information similar to that obtained by the BOLD signal in fMRI, by measuring the absorption of light. This signal is known as the slow signal and is so named because the time course is on the order of seconds: it starts about a second and a half after neuronal activity commences and subsides seconds after it stops. As with the BOLD signal, it is thought to reflect increased blood flow to areas engaged by task demands. However, unlike BOLD, which provides a signal that is based on the ratio of oxyhemoglobin to deoxyhemoglobin in the blood, optical imaging can actually tease them apart, because the degree to which light is absorbed by each of these substances can be determined

separately. For example, meta-analyses of studies of individuals with depression have shown that whereas there are reduced levels of oxyhemoglobin over the frontal cortices of individuals with depression as compared to controls when engaged in cognitive tasks, no such group differences are observed for deoxyhemoglobin (Zhang et al., [2015](#)).

Second, it can measure the scattering of light, which is related to physiological characteristics such as the swelling of glia and neurons that are associated with neuronal firing. This information is known as the fast signal because it occurs simultaneously with neuronal activity (Andrew and MacVicar, [1994](#)). One method, event-related optical signal or EROS, takes advantage of this fast signal to record information locked to an event, much the way ERPs record the time-locked electrical response to a stimulus. The EROS method provides information about the source of activity within millimeters while providing temporal information on the order of milliseconds (typically recorded every 20 ms or so) (for a review see Gratton and Fabiani, [2010](#)). For example, EROS can be used to reveal rapid interactions between posterior and anterior brain regions involved in language (Tse et al., [2007](#)). However, this method has a major limitation: it cannot be used to obtain information about subcortical regions because too much light gets absorbed on the way to and from structures deep within the brain. Current work is continuing to advance its utility to a broader range of questions.

One of the advantages of near-infrared spectroscopy is that it can be used to good effect in populations for whom using fMRI would be difficult or impossible. For example, it is difficult to do fMRI scanning on infants. Obtaining a good image requires the participant to remain still, not a characteristic for which infants are known unless they are sleeping. And as the magnet is noisy, it is difficult to get infants to sleep while in it (Aslin et al., [2015](#)). Another advantage is that it can provide information about oxygenation of the brain, which may be especially important to examine in certain situations, such as determining how the brain is responding after trauma (Weigl et al., [2016](#)).

Techniques for Modulating Brain Activity

Some of the more dramatic methodologies employed in cognitive neuroscience can actually modulate or change brain activity in either clinical populations or neurologically intact individuals. These methods are particularly informative, as they can work either to temporarily decrease or increase brain activity. Unlike brain mapping techniques, such as fMRI and EEG, in which we can only observe correlations with behavioral traits or outcomes, modulating brain activity allows scientists and clinicians to observe cause and effect.

Transcranial Magnetic Stimulation (TMS)

The best of example of this type of approach is [transcranial magnetic stimulation \(TMS\)](#). TMS can be conceptualized as working in a way opposite from MEG. Whereas MEG records the magnetic fields produced by the electrical activity of the brain, in TMS a pulsed magnetic field over the scalp induces an electrical field, which alters the pattern of brain activity in the underlying tissue. This magnetic field is created by a coil or series of coils placed on the scalp. An example of a TMS set-up is shown in [Figure 3.16](#).

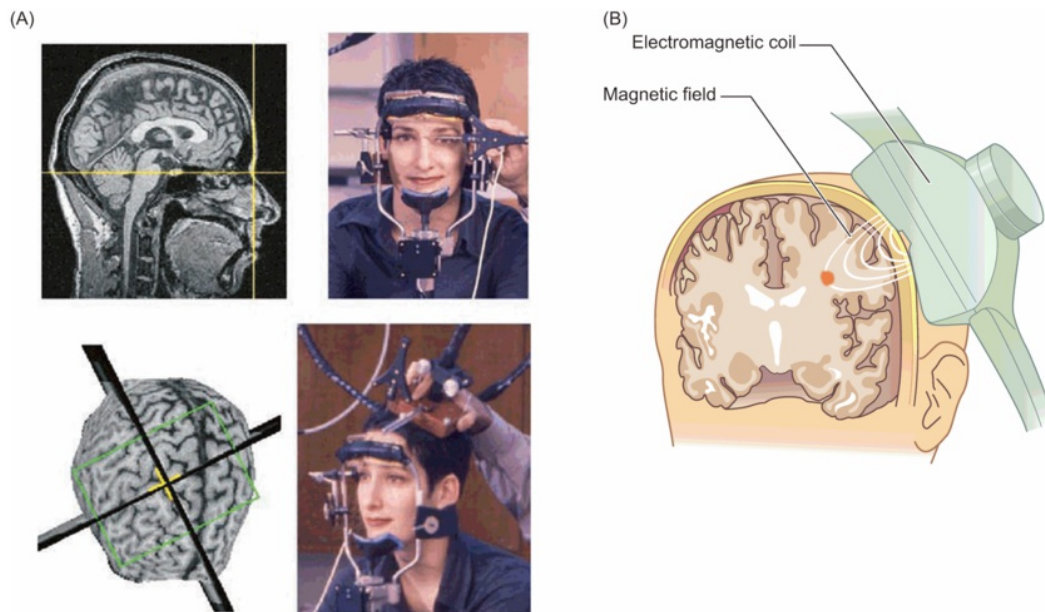


Figure 3.16 Transcranial magnetic stimulation (TMS) can be used to alter ongoing brain activity.

(A) On the left, an experimenter positions a coil over a participant's head. Generally, a structural MRI scan is used to find landmarks on a person's head, which are used as a reference. The person's head is then placed in a stereotaxic frame with regard to such a reference point. Next, the site at which TMS is to be delivered is identified with regard to the person's brain anatomy and then the coil is placed at that coordinate within the stereotaxic frame. (B) A diagram of how TMS affects the brain tissue under which it is positioned.

Source: <http://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/home/ovc-20163795>.

The induced electrical field alters the membrane potential of neurons, causing them to depolarize synchronously, which in turn changes the probability that they will fire. Once the pulsed magnetic field is discontinued, the neurons can return to their previous state. Although TMS has been referred to as causing a “reversible” lesion, which would suggest that it blocks neuronal activity, it is better understood as scrambling neuronal activity – it causes neurons to fire in a random pattern rather than in a coherent manner. In the commonly used version of TMS, the coils affect only the region of the brain

closest to the surface. This means that it is not possible to stimulate deeper cortical neurons or subcortical structures without affecting the neurons that are on top of them, so the method is most effective with regards to cortical structures. However, newer “deep” TMS methods are currently being pursued to allow alteration of function in subcortical regions as well (Bersani et al., [2013](#)).

TMS can be used to either facilitate brain activity or disrupt it depending on the nature of the [pulse sequence](#). For example, TMS applied over primary visual cortex can lead to a transient scotoma (a blind spot in the visual field). Conversely, it can be used to induce phosphenes, which are spots of light within the visual field (for review of the basics of this method, see Siebner et al., [2009](#)).

One of the major advantages of TMS is that it can be used to confirm findings from the lesion method and implicate a brain region as playing a critical role in a specific mental function. If a brain area is critical for a particular mental function, then applying TMS to the region should disrupt that function. For example, PET and fMRI studies have indicated that primary visual cortex becomes active when an individual imagines an object, “picturing” it in his or her mind’s eye (e.g., Kosslyn et al., [1995](#)). But perhaps a different brain area is critical for imagery and the activation in primary visual cortex is the result of feedback from this region. To resolve this ambiguity, researchers applied TMS over primary visual cortex and found that it disrupts visual imagery, indicating that these brain regions are in fact critically involved in producing visual imagery (Kosslyn et al., [1999](#)). Similarly, this technique can be used to provide insights into how the brain reorganizes, either with learning or as a result of sensory deprivation. For example, applying TMS to primary visual areas in normal individuals does not interfere with their reading Braille, an alphabet felt with the fingers. We would anticipate such a result, as reading Braille would of course rely heavily on tactile regions of the brain. However, TMS applied to the visual cortex of blind individuals actually interrupts the reading of Braille (Cohen et al., [1997](#))! Such a finding suggests that as a result of sensory deprivation and exposure to Braille, the visual cortex of blind

individuals has reorganized from processing visual information to processing nonvisual information.

TMS is starting to be used more frequently in therapeutic settings (for review see Wassermann and Zimmermann, [2012](#)). Because of its efficacy in treating depression, successive trains of high-frequency repetitive TMS (rTMS) applied over left frontal regions daily over 4–6 weeks (20–30 sessions) are now approved for use in many countries across Europe, in Canada, New Zealand, Australia, and Israel, and the United States (Lefaucheur et al., [2014](#); Perera et al., [2016](#)). In fact, a meta-analysis across 30 studies performed over more than a decade indicates that this method is an effective treatment and at least as potent as a subset of antidepressive medications (Schutter, [2009](#)).

Because TMS alters brain function, it must be used with caution. Initially studies indicated that both single-pulse TMS in patients (Fauth et al., [1992](#)) and too high a rate of stimulation of rTMS in neurologically intact individuals (Wassermann et al., [1996](#)) could induce seizures. On a less severe level, in humans TMS can lead to mild headache (due to activation of scalp and neck muscles), muscle twitches, or nausea. Therefore, it must be utilized very carefully, and strict guidelines have been drawn up to minimize the potential for such adverse effects (Wassermann, [1998](#)). These guidelines appear to be effective, as recent research reveals only mild side effects both in neurologically intact control groups (Anderson et al., [2006](#)) and in patients with clinical conditions such as depression (Janicak et al., [2008](#)).

Transcranial Direct Current Stimulation (tDCS)

An associated method, transcranial direct current stimulation (tDCS), avoids some of these issues because the stimulation is orders of magnitude lower than in TMS and it is well tolerated with few side effects (e.g., Russo et al., [2017](#)). In this method, a weak electrical current runs through the scalp, skull, and brain between an entrance electrode and an exit electrode. If the brain area stimulated is below the anodal (i.e., positive) electrode, neuronal activity is increased. On the other hand, if the brain area stimulated

is below the cathode (i.e., negative) electrode, neuronal activity is decreased. As with TMS, one can use the method either to try to disrupt activity and create a “virtual lesion” via cathodal stimulation or to enhance activity via anodal stimulation. Compared to TMS, the stimulation is not only less intense, but also much less focused in terms of the brain area affected. As such, this method not as helpful with regards to enabling linkages between specific brain regions and behavior (see [Figure 3.17](#)).

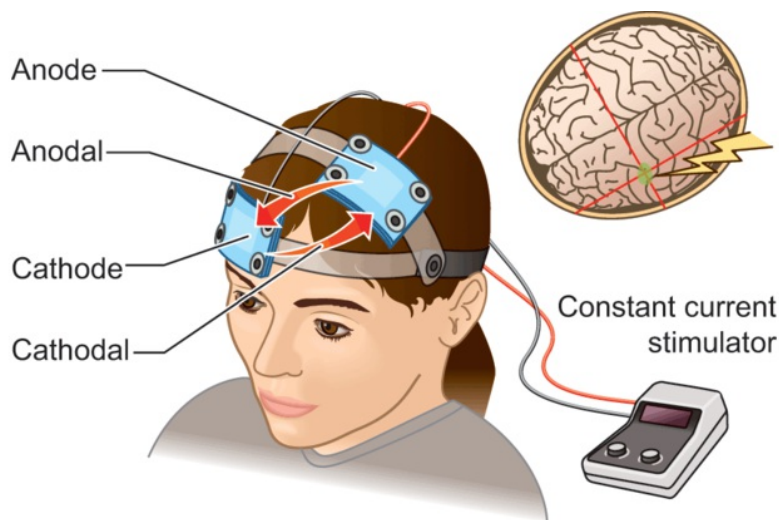


Figure 3.17 An example of the set-up for transcranial direct current stimulation.

In this system, there are two large electrodes placed on the brain, one which is positive (anodal) and one of which is negative (cathodal). Current is run from one electrode and the current courses through to the other. Brain activity is increased if stimulation occurs at the anode, but decreased if stimulated at the cathode.

Source: <http://jamanetwork.com/data/Journals/NEUR/22588/nmr80008f1.jpg>.

Nonetheless, due to its ease of use and the relatively small side effects and general overall safety of the method (Bikson et al., [2016](#)), tDCS is being used in a variety of clinical and experimental settings. This method of brain stimulation is being used to determine whether it can help in reducing cravings associated with substance use disorders (Spagnolo and Goldman, [2017](#)), to delay or avoid a transition to Alzheimer’s disease in elderly individuals who are showing cognitive decline (Birba et al., [2017](#)), and to reduce auditory hallucinations associated with schizophrenia (Pondé et al., [2017](#))

among other psychiatric disorders (for review see Philip et al., [2017](#)). Another area where it is receiving much use is with regards to language recovery after stroke (Monti et al., [2013](#)). This work has suggested that it is likely that tDCS is helpful, although many issues regarding the duration and intensity of treatment, those individuals who will most benefit, and whether the stimulation should or should not be given while the person is performing the cognitive process that is to be modified (e.g., speech output) remain to be determined (de Aguiar et al., [2014](#)).

Interestingly, tDCS has also been found to improve memory, attention, and other abilities in neurologically normal individuals (Coffman et al., [2014](#)). This has led to a discussion of the ethical issues surrounding brain “enhancement” when no clinical syndrome is involved (Voarino et al., [2016](#)) (see also Chapter 17, pages [534–535](#)). There are concerns because obtaining or creating such a tDCS system is so relatively easy that people are creating their own “do-it-yourself” systems and protocols to try to improve their mental abilities, such as increasing their video-game performance. However, there is concern of misuse of the self-administration of this technology in neurologically normal individuals without clear knowledge of the long-term effects of such stimulation, especially in unconstrained situations (Jwa, [2015](#)). Thus, while these methods seem to be highly promising in clinical populations, the degree to which they will be effective in and appropriate for neurologically normal individuals remains to be seen.

In summary, in this section we discussed various techniques for assessing or modulating brain function. Because we need the proper tool for the job, the relative advantages and disadvantages of each method must be considered for each question to be investigated. A summary of the information provided by each method, as well as its spatial and temporal resolution, is presented on the inside back cover of this book. [Table 3.5](#) lists the advantages and disadvantages of each method.

Table 3.5 Advantages and Disadvantages of Different Methods Used in Cognitive Neuroscience

Methods of Assessing Brain Anatomy

| | ADVANTAGES | DISADVANTAGES |
|--|--|--|
| CAT (computerized axial tomography) | Can be used with almost all individuals | a. Involves the use of ionizing radiation b. Does not provide high spatial resolution |
| Anatomical MRI (magnetic resonance imaging) | a. Can be used to detect different substances b. Allows white-matter tracts to be visualized via diffusion weighted imaging c. Does not involve radiation. Good spatial resolution | a. Cannot be used with individuals who have metal in their bodies or pacemakers b. Can induce claustrophobia in some individuals |

Methods of Assessing Brain Physiology

| Functional Brain Imaging | ADVANTAGES | DISADVANTAGES |
|--|--|--|
| PET (positron emission tomography) | Can be used to assess many aspects of physiological function | a. Involves the use of ionizing radiation (which limits an individual to 4–5 scans per year) b. Provides images that are averaged over times longer than thought processes require |
| MRS | a. Provides information about | a. Limited to only a certain |

| | | |
|-----------------------------------|--|---|
| (magnetic resonance spectroscopy) | neurochemical processes | subset of compounds that are found in large concentrations in the brain |
| | b. Does not involve the ionizing radiation associated with PET | b. Information must be gathered from a large region of brain tissue, so that precise localization is not possible |
| fMRI | a. Provides good spatial resolution in relatively short periods | a. Cannot be used with individuals who have metal in their bodies or pacemakers |
| | b. Can be performed repeatedly on the same individual | b. Limited ways of measuring physiological function |
| | c. Widely available | BOLD: (1) Provides information only on relative oxygenation of the blood; (2) measures the brain's hemodynamic response that occurs on the order of seconds |
| | d. Can be analyzed in a variety of ways to examine brain networks and brain connectivity | |

| Electromagnetic Recordings | ADVANTAGES | DISADVANTAGES |
|------------------------------|---|--|
| Single-cell | Provides information on the type of stimulus to which a cell responds | Cannot be used in humans except under very specific circumstances |
| EEG (electroencephalography) | a. Provides information on the general state of the person (e.g., alert, drowsy) b. Provides excellent | a. Difficult to determine the source of activity from within the brain. Difficult to detect activity of cells oriented parallel to the brain's surface |

temporal resolution

ERP (event-related potentials)

- a. Provides information that has been linked to specific psychological processes such as memory and attention
- b. Provides excellent temporal resolution

a. Difficult to determine the source of activity from within the brain. Difficult to detect activity of cells oriented parallel to the brain's surface

MEG (magnetoencephalography)

- a. Provides better information than EEG/ERP about the source of the signal
- b. Not as susceptible to differences in conduction of tissue intervening between the brain and scalp

a. Set-up is large and elaborate, requiring a shielded room. Cannot detect cells with orientations radial to the brain's surface

Optical Imaging

ADVANTAGES

DISADVANTAGES

Slow signal (metabolic)

- a. Noninvasive
- b. Inexpensive
- c. Portable
- d. Allows the concentration of oxygenated and deoxygenated blood to be calculated separately

- a. Cannot provide information on subcortical structures
- b. Can measure only the hemodynamic response of the brain

| | | |
|---------------------|--|---|
| Fast signal EROS | <ul style="list-style-type: none"> a. Noninvasive b. Inexpensive c. Portable d. Detects a neuronal response rather than a hemodynamic response | <ul style="list-style-type: none"> a. Cannot provide information on subcortical structures |
|---------------------|--|---|

Methods of Modulating Brain Activity

| | ADVANTAGES | DISADVANTAGES |
|--|--|---|
| TMS (transcranial magnetic stimulation) | <ul style="list-style-type: none"> a. Can be used to confirm findings from lesion method b. Can be used therapeutically to treat clinical syndromes c. Can provide information on brain reorganization d. Provides information about the functional connectivity of brain regions. Can be used to determine whether a deficit results from dysfunction of a region or disconnection of brain regions | <ul style="list-style-type: none"> a. Very small but possible potential for adverse effects on brain functions (e.g., induce seizures) b. Can only stimulate regions close to the surface c. Does not allow for precise localization of effects but better than tDCS |
| tDCS (transcranial direct current) | <ul style="list-style-type: none"> a. Is relatively easy and portable to use | <ul style="list-style-type: none"> a. Only provides diffuse stimulation to the brain and hence cannot be well directed to |

stimulation) b. Is less powerful than TMS specific brain regions
and hence is generally well
tolerated

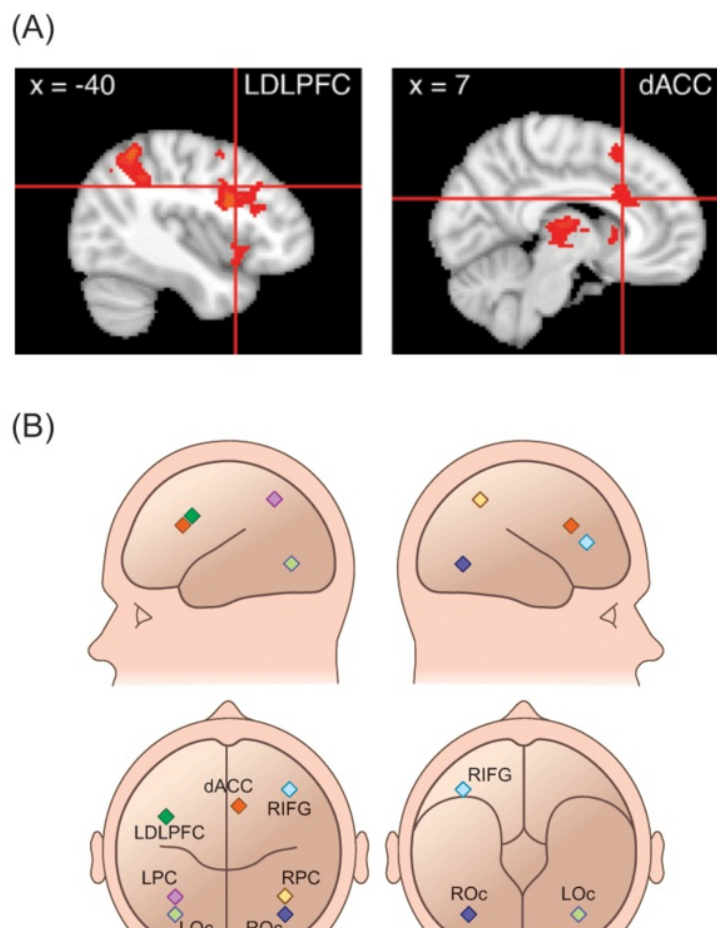
Multilevel and Multi-modal Approaches

As [Table 3.4](#) shows, there is no one perfect method that can provide a cognitive neuroscientist with answers to all questions of interest; each method has its advantages and drawbacks. In recent years, researchers have started to use a multilevel or multimodal approach, using multiple tools in tandem. In probably the most common case, researchers try to combine information from two measures derived from the same technique. Scientists can examine the relationship between measures of brain anatomy derived from MR imaging as well as measures of brain function derived from fMRI to provide information that is not available through either one alone. For example, research has shown that individuals with schizophrenia can be distinguished from controls because the correspondence between neuroanatomical measures of connectivity as indexed by diffusion tensor imaging and functional measures of connectivity as indexed by resting-state MRI is lower in individuals with schizophrenia than controls, suggesting a less coherent or more disrupted brain organization in schizophrenia (Skudlarski et al., [2010](#)).

Bridges can also be made between quite distinct modalities in an attempt to use them in tandem because they provide complementary information. As we have already discussed, one common coupling combines electromagnetic methods of recording brain activity, which provide excellent information about the timing and sequence of brain events, with fMRI, which is better at providing information about the location of brain activity. In some cases, both types of information may be very important for the question under investigation.

For example, as we will learn in [Chapter 10](#), attention is supported by a circuit of brain regions. One theory argues that certain parts of this circuit exert control over other

parts of the circuit. Although fMRI can do an excellent job of identifying all the portions of the circuit, it cannot identify which one of the regions acts first and which one acts second. To demonstrate that certain portions of the circuit lead and other portions follow requires a tool that provides information about the timing of the neuronal response, such as ERPs. In such approaches, individuals perform the task while being imaged in an MRI machine, and the localization of activity is observed. Then either concurrently (although it is technically difficult to record EEG in an MR environment), or in a separate session, EEG is recorded while performing the same task. In such cases, the data obtained from fMRI about the location of brain activity during a mental process are utilized to constrain the set of possible locations for the possible dipoles. The researcher can then examine whether the ERP data collected on the scalp are consistent with such a dipole. If there is a good fit, the researcher has information about both the probable location and the time course of a given mental process (see Silton et al., [2010](#), for an example of such an approach) (see [Figure 3.18](#)).



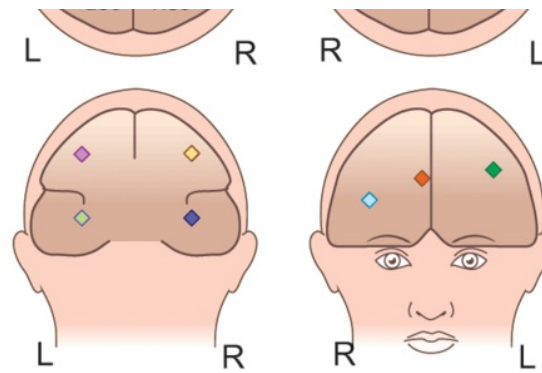


Figure 3.18 Dipole-source modeling using fMRI data.

This study focused on the relationship in time between activity in the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC). (A) Areas of activation within each of these regions for the condition of interest as ascertained from fMRI. (B) Dipoles are placed in the regions identified by fMRI along with dipoles in other regions of the brain that are expected to be active during the task. For example, dipoles are placed in right occipital (ROc) and left occipital (LOc) regions since this is a visual task and activity will also be generated by brain tissue in that area. As such, the signal recorded on the scalp will also reflect activity from dipoles in those regions as well from dipoles in the regions of interest, DLPFC and ACC.

Another multi-method approach involves combining TMS with other methods to provide information on the connectivity between brain regions. The logic underlying these studies is to decrease or interrupt activity of one brain region using TMS, and then to examine the change in the pattern of activity across the whole brain with another imaging method, such as PET or fMRI. Those brain regions intimately connected with and influenced by the region receiving TMS should also show decreases in activity.

As an analogy, imagine that I want to determine which students in the class tend to talk to one another. I could temporarily disable the cellular phone of one person in the class, much in the way TMS can disrupt the activity of a single brain region. I can now determine which individuals in the class talk to the person whose phone has been disabled, by examining which individuals are receiving fewer phone calls than normal. In the case of the brain, PET or some other method is used to determine which brain

regions are showing a decrease in activation (rather than, in our analogy, a decrease in phone calls received). This logic has been utilized very effectively by researchers. For example, rTMS over left mid-dorsolateral frontal cortex has been linked to modulation of activity in limbic and cingulate regions as measured by PET (Paus et al., [2001](#)), which appears to be one of the mechanisms by which rTMS alleviates the symptoms of depression (Paus and Barrett, [2004](#)). Recently, TMS has been used together with ERPs to similar effect (see Taylor et al., [2008](#), for a longer discussion of using ERPs and TMS in conjunction).

Because the interconnectivity and functional interrelations between brain regions are sources of major unanswered questions in cognitive neuroscience today, TMS has an important role to play in increasing our understanding of the organization of the human brain. For example, researchers can stimulate a brain area with TMS and then using functional MRI determine which brain areas show reduced (or increased) activity compared to a no-stimulation baseline. The notion here is that if a given region is “talking” to other regions, then altering activity in that region has consequences for activity in other regions with which it is communicating, but not for regions with which it is not connected (Hampson and Hoffman, [2010](#), for review). For example, giving TMS over regions of the frontal cortex involved in eye movements, which help to direct our eyes to a location to which we are paying attention, leads to decreases in activity in parietal regions that are involved in attentional control as well. Moreover, the degree to which connectivity is decreased between these regions as a result of TMS predicts the degree to which study participants showed a deficit in the ability to shift their attention to new region of space (Heinen et al., [2017](#)).

You may wonder why researchers do not use multi-modal techniques as a matter of course – it would seem the best way to answer questions. Unfortunately, multi-method techniques usually require using at least twice as much equipment, collecting and analyzing twice as much data, undertaking additional analyses to link them together, and often the cooperation of research participants to do multiple sessions of similar tasks in

each modality. The benefits of a multi-modal approach, in terms of the additional knowledge that can be gained, must justify the effort required.

Combining Computational and Neuroimaging Approaches

In this final section of the chapter, we discuss another major method in cognitive neuroscience, the use of computational modeling techniques, and discuss how they can be used to great advantage in conjunction with neuroimaging.

There are a variety of models that can be implemented, from formal models that take a standard mathematical form (e.g., $y = ax + b$) to [connectionist networks](#), which are composed of interconnected layers of units that exhibit neuron-like behavior (O'Reilly et al., [2012](#)), to machine-learning techniques that allow replicable patterns to be discovered in data and generalized to new situations or conditions. What is most notable about these latter two types of models is their ability to “learn” without being provided specific rules, a property that simulates important aspects of human cognition. For example, you had actually learned the grammar of your native language long before you studied it in school, and no one taught you the “rules.” Rather, your brain somehow extracted the regularities of language without formal training. These [computational models](#) learn in much the same manner: by extracting the regularity of relationships with repeated exposure.

Here we provide just a couple of examples of how these methods can be useful (see Cohen et al., [2017](#) for recent review). First, we discuss research using formal models in which a mathematical formula is used to predict behavior. One example of such an approach is a model that is designed to predict, in a gambling situation, whether an individual will decide to “play” a card for the chance to win (or lose) money, or “pass” because they think a negative outcome is likely. In this model, it is assumed that the person’s decision on any given trial is based on three factors (or parameters in the model): (a) the relative degree to which that person is sensitive to loss compared to

gains; (b) how far the person looks back, that is, are they, for example, just considering the very last outcome or are they integrating over, say, the past four outcomes; and (c) the degree to which an individual's behavior is influenced by the feedback, that is, do they stick with one way of responding (e.g., always play) or do they pass after every loss and play after every win (Stout et al., [2004](#)). This model can predict a person's behavior on a given trial much as if I provide you with a model that says $y = 2x + 1$, and I give you a value of 5 for x , you would predict that the value for y would be 11. One can then determine whether particular areas of the brain show activation that trial-by-trial follows a similar pattern as predicted by the model. To be more concrete, if my model is $y = 2x + 1$, then given values of 5, 3, and 4 for x , I would predict values of y of 11, 7, and 9. Hence researchers can see if certain brain regions show a similar pattern of activity, in this case going from high to low to medium.

Notice here that we are not just examining whether the activity in a particular brain region is high or low. Rather, it has been shown that brain areas innervated by dopamine, such as the ventral striatum, seem to show this pattern over time, tracking information with reward and decision making (Schultz et al., [1997](#)). Hence, rather than just saying that the ventral striatum is active during decisions about reward and punishment, we can make a more fine-grained and nuanced suggestion that this brain region is involved in predicting the likely outcome so as to influence behavior.

These models can be taken even a step further to try to understand what is disrupted in individuals with certain disorders, such as substance use disorder, who sometimes show altered activation in reward-related regions. Such formal models indicate that while activity of [orbitofrontal cortex](#) in neurologically normal individuals follows predictions of the model, it does not do so in individuals with substance use disorder (Tanabe et al., [2013](#)). Such a finding suggests a potential reason that such individuals with substance use disorder seem to be relatively impervious to the deleterious nature of their decisions: it may be that their brains are not correctly computing the likely outcome of their behavior.

Other approaches use machine-learning techniques to “discover” patterns of brain activity associated with certain behavioral states, which then in turn can serve as biomarkers of particular processes (Woo et al., [2017](#)). For example, such an approach has identified a pattern of activity over the brain, known as a classifier, that can predict the degree to which a person is in pain. These classifiers do not just contain information about whether a particular brain region is active or not during pain. Rather, they determine which brain regions track the degree of pain a person is feeling, and are active during pain but not other states.

The predicted degree of pain is not a simple additive calculation across these brain regions. Rather, different regions provide different weighting, some influencing the final outcome more and others less. Notice, this is a much more sophisticated picture of the brain’s response to pain – it is not saying Areas A, B, and C are active. Rather, it suggests that the perception of pain is associated with a specific pattern of activation across the brain and that the relative contribution of activation in any given region can vary so as to contribute to the brain’s final perception of pain. The brain regions that contribute to this neurologic signature of pain are shown in [Figure 3.18](#).

Importantly, this brain “signature” is quite consistent across individuals, so much so that although the signature was originally deduced from a specific set of participants, it has been found to be successful in predicting pain across new and different groups of people (Wager et al., [2013](#)). In addition, while this overall signature occurs whenever a person is in pain, subtle but detectable differences can reveal the source of the pain, for example, whether it is a physical pain induced by a hot object on the skin, or the picture of an ex-partner who broke your heart (Woo et al., [2014](#)).

Having such a “biomarker” or signature of pain not only provides important information about the brain basis of pain, but also can be used for example to determine the efficacy of drugs or compare pain levels across people. For example, while one person may be scared of pain and rate a pin prick as a “5” on a 1–10 scale of pain, most people would only rate it as a “2.” As such, these computational techniques open up a

host of new questions that can be asked by cognitive neuroscientists and in a more sophisticated way. In addition, they are beginning to provide the opportunity to take brain imaging data and use it in novel and interesting ways in clinical settings.

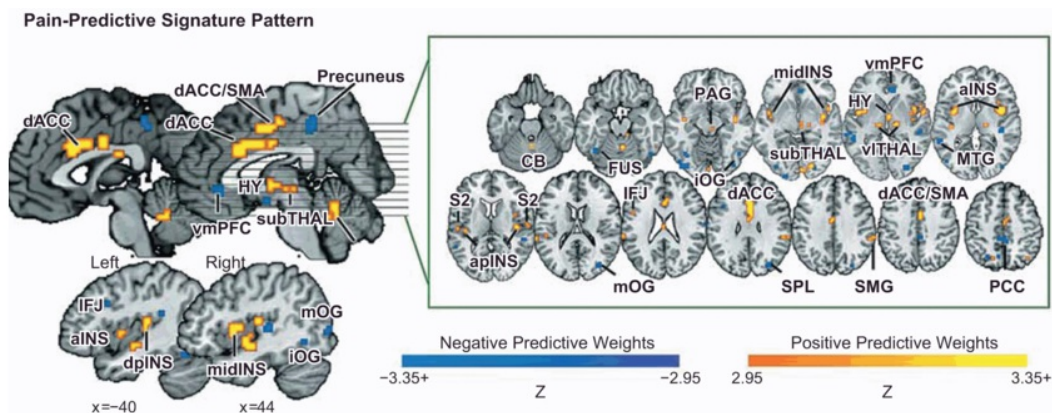


Figure 3.19 Brain regions that contribute to a neurological signature of a mental state - pain.

Shown here are the regions whose activity contributes to the sensation of pain. Areas shown in a warm color are those that when active are associated with a greater feeling of pain, whereas activity in those shown in blue are associated with a reduced sensation of pain.

(from Wager et al., [2013](#))

Obviously, a vast array of tools is available to cognitive neuroscientists as they work to discover how the neural organization of the brain influences how we think and what we feel. In subsequent chapters, the experiments we discuss will utilize the broad span of techniques discussed in this chapter. These methods are somewhat complicated and you may need to flip back to this chapter to remind yourself of what these methods can and cannot tell us. Knowing the strengths and limitations of each method will help you to evaluate the strength of the experimental evidence discussed in the remaining chapters of this book.

Summary

Introduction

- The relationship between the functional architecture of the brain and behavior can be investigated through the use of a variety of populations and techniques. Depending on the question researchers want to answer, the focus may be on the neuroanatomy or neurophysiology of the brain, or on the way in which the brain affects behavior.
- Various techniques are often used in combination because converging evidence from different techniques is the most powerful tool for uncovering fundamental aspects of brain-behavior relationships.

Populations of Research Participants

- Patients with delineated brain damage allow researchers to determine which functions are lost as a result of damage to specific brain regions. This method cannot identify all brain regions that participate in a function, but rather identifies only the areas critical for task performance.
- Neurologically intact individuals provide (1) a baseline against which to compare performance of individuals who sustain brain trauma, (2) information on the basic neuroanatomical organization of the brain, and (3) when used in conjunction with brain imaging techniques, evidence on how brain structures work together.

Techniques for Analyzing Behavior

- Cognitive theories play a large role in helping to dissect the different component processes of mental functioning.
- Clinical assessment of behavior is done either via a test battery that samples a large number of mental functions without going into a detailed examination of any one function, or a customized approach that assesses very specific cognitive

functions in addition. In either case, a measure of general intelligence often also is obtained.

Techniques for Assessing Brain Anatomy

- Magnetic resonance imaging works by perturbing hydrogen atoms and deriving information about different characteristics of brain tissue, such as water and fat, by determining the time it takes them to return to their original state at each point of the brain.
- As such, magnetic resonance imaging provides information about brain structure that can be tuned to gray matter or to white matter.
- MRI can provide information not only on brain volume, but also cortical thickness and cortical surface area, as well as the shape of subcortical structures.
- White-matter connectivity between distant brain regions can be assessed by diffusion weighted imaging.

Neurochemical Methods

- Functional brain imaging methods provide information about the physiological activity in the brain that occurs as a by-product of neuronal firing, and thus provide very good information about where in the brain activity is occurring.
- Positron emission tomography (PET) uses a radioactively tagged molecule to provide a measure of physiological activity of different brain regions. It can be used to examine consumption of glucose and oxygen as well as binding of specific neurotransmitters.
- Magnetic resonance spectroscopy provides information about a limited set of compounds, such as the neurotransmitters glutamate and GABA. In general due to the small signal associated with such compounds, information can only be gleaned over a relatively large area of brain tissue.

- Functional magnetic resonance imaging (fMRI) works by detecting differences in the magnetic properties of oxygenated and deoxygenated blood, called the BOLD (Blood Oxygen Level Dependent) signal. This signal identifies brain regions where neurons are active because the vascular system provides abundant oxygen to those areas reducing the amount of deoxygenated blood in that region.
- BOLD-related information can be obtained either while individuals are performing a task or while they are at “rest,” typically staring with eyes open at a fixation cross.
- In addition to obtaining information about the degree of activation in a given brain area, the fine-grained pattern of activity can provide detail on the type of information that is being represented by the brain (e.g., a fruit versus a tool).
- Brain connectivity can be assessed in a variety of ways. Scientists can design a seed region and determine which brain region appears to show a similar pattern of activation over time. Another approach is to use graph theory to treat the brain as a complicated network with subnetworks and hubs that are central points of information flow. Still another approach, independent components analysis, treats the brain as if it were composed of networks or “groups” of regions whose activity follows a coherent pattern across time, and which differs from other networks.

Techniques for Revealing When Activity Is Occurring: Electromagnetic Methods

- Electromagnetic recording methods record the electrical signals or the magnetic fields that accompany neuronal firing, providing very precise information on when neuronal activity is occurring.
- Electroencephalography (EEG) is used to examine the frequency of the summed electrical signal of synchronous firing in the dendrites of populations of neurons.

It is useful for distinguishing states of alertness, drowsiness, and sleepiness and can be used for detecting the electrical spiking that occurs in epilepsy.

- Event-related potentials (ERPs) are electrical potentials that are recorded in response to an event and are time-locked. Different portions of the ERP signal are linked to specific sensory or cognitive processes.
- Magnetoencephalography (MEG) provides information about the magnetic potentials that are associated with electrical activity in the brain. Different portions of the MEG signal are linked to specific sensory or cognitive processes.
- Recent research has focused on time-frequency analysis in which particular the distribution of distinct frequency bands of EEG activity is examined over time. In addition, the relationship between the oscillatory nature of these frequency bands across brain regions is examined to provide information on brain connectivity.

Optical Recording Methods

- Optical recording methods supply information about the absorption and scattering of light through the brain. These can be used to infer regional changes in oxygenated and deoxygenated blood that occur on the order of seconds, and information about changes associated with neuronal firing that occur on the order of milliseconds.

Techniques for Modulating Brain Activity

- Transcranial magnetic stimulation (TMS) disrupts brain activity through magnetic fields on the scalp that interfere with the electrical firing of neurons. It can be used to identify those regions of the brain that are critical to performance of a task. Repetitive TMS (rTMS) can also be used to augment brain activity and is used therapeutically.

- Transcranial direct current stimulation (tDCS) uses a small amount of current and only two electrodes to either increase or decrease brain activity. Its effects are more diffuse than TMS but since they are weaker may have advantage in certain experimental and clinical situations.

Multi-modal and Multimethod Approaches

- Because each method used in cognitive neuroscience has its drawbacks or limitations, scientists may try to use multimodal approaches, such as using structural and functional MRI in tandem. They may also use multimethod approaches combining, for example, fMRI because it provides information on where in the brain processing happens along with electrophysiological methods that provide information on when processing occurs.

Combining Computational and Neuroimaging Approaches

- Recent approaches have used sophisticated computational models to try to find more refined information above and beyond how much the brain is activated in any given condition. These methods may determine which brain regions track the outcome of models that, for example, provide the likelihood of receiving a reward. They may also help to define the pattern of activation across the whole brain that can predict the degree of a psychological state of an individual, such as the person's level of pain.

Part II



Neural Bases of Mental Functions

Chapter 4 [Motor Control](#)

Chapter 5 [Sensation and Perception](#)

Chapter 6 [Object Recognition](#)

Chapter 7 [Spatial Cognition](#)

Chapter 8 [Language](#)

Chapter 9 [Memory and Learning](#)

Chapter 10 [Attention](#)

Chapter 11 [Executive Function and Higher-Order Thinking](#)

Chapter 12 [Emotion](#)

Chapter 13 [Social Cognition](#)

Chapter 4

Motor Control



[Introduction](#)

[Peripheral Control of Movement](#)

[Motor Tracts](#)

[Brain Structures Involved in Motor Control](#)

[Subcortical Regions](#)

[Cerebellum](#)

[Basal Ganglia](#)

[Cortical Regions](#)

[Primary Motor Cortex](#)

[Supplementary Motor Complex and Premotor Areas](#)

[Anterior Cingulate Cortex](#)

[Right Inferior Frontal Cortex](#)

[Parietal Lobe](#)

[Integrated Models of the Motor System](#)

[In Focus: Using Brain Activation to Control Prosthetic Limbs](#)

[Motor Disorders](#)

[Subcortical Motor Disorders](#)

[Parkinson's Disease](#)

[Huntington's Disease](#)

[Tourette's Syndrome](#)

Cortical Motor Disorders

Dichotomous Classifications of Apraxia

Lesions That Lead to Apraxia

Other Varieties of Apraxia

Summary

The life story of Muhammad Ali, one of the twentieth century's most famous boxers, interweaves not only boxing and politics, but also the neural basis of motor control. Ali, who was known as Cassius Clay before his conversion to Islam, rose to prominence as an Olympic boxer. He eventually turned pro and became a world champion. Ali said that his boxing strategy was to "float like a butterfly, sting like a bee," meaning that his fancy footwork allowed him to flutter around the ring evading his opponents' punches until he could move in for a knockout. At the height of his career, Ali was drafted to serve in the United States armed forces in Vietnam, but he refused induction because of his religious beliefs. Convicted of draft evasion, he was stripped of his crown, and not allowed to box in a sanctioned match for the next three years.

During his exile from the ring, Ali's ability to "float" deteriorated substantially. When he was allowed to resume his boxing career (shortly before the Supreme Court overturned his conviction), he adopted a different fighting style that capitalized on the strength he had gained during his hiatus from professional bouts. This new style, however, would have deleterious effects later in his life. Ali would let an opponent get him against the ropes in the early rounds, either blocking or absorbing an onslaught of punches that would have felled most men. This technique became known as the "rope-a-dope" style, because a boxer was traditionally considered a fool if he allowed himself to get caught against the ropes. However, Ali would patiently wait for the later rounds

when his foe was exhausted, frustrated, and getting sloppy. Then he would throw the punch that sent his opponent reeling to the mat.



Figure 4.1 Muhammad Ali, the boxer, receiving a blow to the head from his opponent, Alfredo Evangelista.

The repeated punishment that Ali endured in receiving such blows, over the course of his boxing career, led him to exhibit symptoms related to Parkinson's disease after retirement.

After his retirement from boxing, Ali became a popular speaker on the lecture circuit. As time passed, however, people began to notice that he was slurring his words and stumbling. When signing autographs, he was slow and his penmanship became less and less legible. Naive observers assumed that Ali was drunk, but heavy drinking was never his style. Medical examinations revealed that Ali had sustained neurological damage and was most likely displaying signs of Parkinson's disease.

In Parkinson's disease, motor control is disrupted so that previously simple motor acts become extremely difficult. The four basic attributes of Parkinson's are slowness of movement, rigidity of movement, postural instability, and tremors – rhythmic, oscillating movements (which are usually observed when a person is at rest). Generally, Parkinson's is observed in older people as a progressive neurological disorder. But Ali, although well past the years when most boxers are in the ring, was only middle-aged. So what could explain these symptoms?

As best his neurologists could surmise, years of boxing had taken their toll on Ali. Although he had never been knocked out, the barrage of punches Ali absorbed with his rope-a-dope style had the cumulative effect of damaging regions of his brain important for motor control. As we discuss later in this chapter, Parkinsonian symptoms begin to manifest themselves when a substantial proportion of the dopaminergic neurons in the substantia nigra are destroyed. As cells die, the remaining cells try to do all the work, but at some point the amount of damage is too great to be compensated for and motor control deteriorates. Thus, although Ali sustained the damage during his long and illustrious boxing career, only afterward did the effects of this damage become apparent (Hauser, [1991](#)) (Lipsyte [20116](#)).

Introduction

Muhammad Ali's Parkinson's disease was caused by destruction to just one of the many brain regions that permit the great diversity of motor skills that humans display. Before we discuss these various brain regions, let us first consider some of the types of movements that people can exhibit. In some motor acts, such as hitting a tennis serve, you must coordinate movement of the gross and postural muscles in a smooth and seamless fashion. When learning to serve, you break down the process into a series of steps: Start to toss the ball, dip your legs, bring the racquet behind your back, push up on your legs, extend the racquet skyward, rotate your torso, and hit the ball. Consider how different such a step-by-step process is from the smooth, well-learned tennis serve of professionals like Serena Williams and Novak Djokovic. Rather than a concatenation of separate movements, the swing of a tennis pro or even a good amateur player appears to be one smooth, continuous motion. As we learn later in this chapter, such smooth, rapid movements are aided by the cerebellum.

Other actions require fine movements. Touch-typing (i.e., when you type with 10 fingers instead of pecking with two), unlike a tennis serve, requires little gross muscle movement because the position of your hands remains relatively static. Typing also requires another skill often seen in motor control, which is that the timing of transitions between movements is critical. For example, typing speed is increased by reducing the time between individual keystrokes. One way to accomplish this increased speed is to adjust the typing of a given key on the basis of the keystrokes that precede and follow it. Our ability to make such adjustments implies that we create an overall motor plan of the series of movements that we want to produce, then invoke this plan when a series of finger strokes is executed. As we learn later, these motor plans are produced by a specific brain region known as the [supplementary motor area](#). This area transmits information about the [motor program](#) to other brain regions, eventually allowing activation of the specific muscles required to execute the program.

In other motor acts, performance is linked to specific external cues, such as when you press on the gas pedal upon seeing a green light and step on the brake upon seeing a red one. When movements require us to break well-learned habits or overcome our

normal associations (e.g., pressing the gas pedal for a red light and stepping on the brake for a green one), or when movements are novel or less well rehearsed, the [anterior cingulate](#) plays a role.

Motor acts often involve multiple brain regions because they require many types of motor control to occur simultaneously, such as control over both the fine and gross muscles. However, as this brief introduction should illustrate, specific brain regions play a more prominent role in certain motor acts than in others. We begin this chapter by reviewing the major brain regions involved in motor control and by pointing out the key contribution each makes. Afterward, we examine clinical syndromes in which motor processing is disrupted. These syndromes fall into two major categories: those resulting from damage to subcortical regions of the brain and those resulting from damage to the cortex. The subcortical syndromes that we discuss – Parkinson's disease, Huntington's disease, and [Tourette's syndrome](#) – all involve a disruption in the form of movements. These syndromes may lead to slowness or imprecision in movement, or to movement that should not occur (e.g., tremors). In contrast, the cortical syndromes impair the conceptualizing, planning, and sequencing that underlie learned movements. In these cases, individuals have difficulty playing the piano or knowing how to program muscles to salute.

Peripheral Control of Movement

Before discussing the role of different brain regions in motor control, we must first understand the basic underlying mechanism that makes our muscles move. Muscles are composed of muscle fibers that can be either in a contracted or an uncontracted state. Muscle fiber contraction is caused by an electrical impulse from a motor neuron whose cell body resides in the ventral portion of the spinal cord. Typically, one motor neuron innervates a number of muscle fibers. The number of muscle fibers innervated can vary from two or three, for muscles involved in very fine motor control, to more than a hundred for large muscles that help us fight gravity, such as the muscles of the leg that

keep us standing. A motor neuron and the muscle fibers it innervates are referred to as a **motor unit**. The synapse between a neuron and muscle fibers is larger and has a more specialized structure than a typical synapse. It is called the **neuromuscular junction** (see [Figure 4.2](#)). For muscles to move, information must be relayed from the nervous system to the muscles across the neuromuscular junction. When this relay is interrupted, paralysis occurs. This pattern is repeated at each level of the spinal cord, but for different areas of the body (refer back to [Figure 1.7](#)).

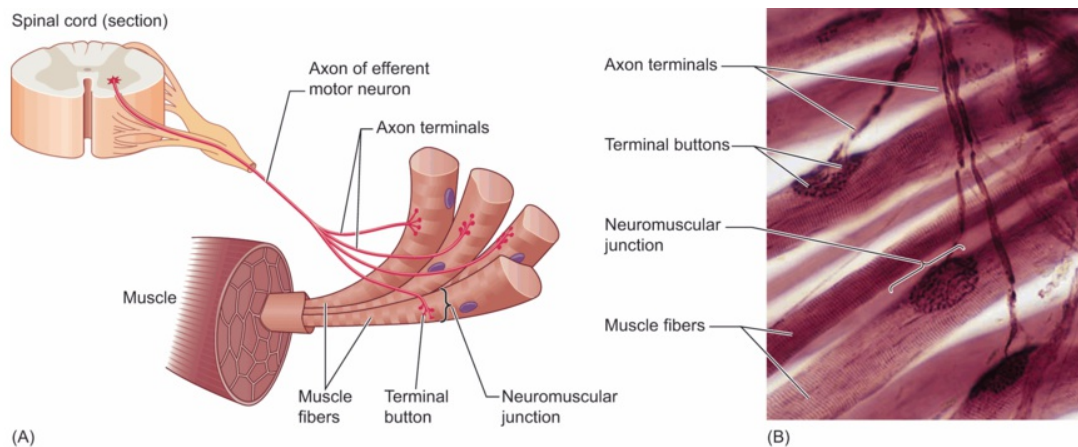


Figure 4.2 The neuromuscular junction.

The cell body of a motor neuron originates in the ventral portion of the spinal cord. It travels along a spinal nerve to the muscles it innervates. When the axon reaches a muscle, the motor neuron divides into many axon terminals, providing a series of unique connections with each muscle fiber, an area known as the neuromuscular junction. Within each neuromuscular junction, the axon terminal further divides into fine branches, each of which ends in a terminal button. When an action potential reaches the terminal button, acetylcholine is released into the synaptic cleft. Acetylcholine then binds with nicotinic cholinergic receptors in special troughs in the membrane of the skeletal muscle, known as motor endplates. This causes an action potential in the muscle membrane, resulting in muscle contraction.

Motor Tracts

Movements planned in the brain need a way to reach the target muscles that execute those movements. This information is relayed along pathways known as motor tracts. To better conceptualize the role these pathways play in motor control, we might consider them akin to the messenger that carries information to the infantry in the army (in this case the muscles), which carries out the orders but does not create or initiate them. Instead, the subcortical and cortical regions that we discuss later are the key regions for determining the form, sequencing, and planning of these movements. The subcortical regions can be thought of as lieutenants who make sure that their platoons are moving along in proper form, whereas the cortical regions are more like generals who plan the actions of vast numbers of platoons.

Two major sets of pathways link the brain to muscles (see [Figure 4.3](#)). The first of these are the lateral pathways, whose cell bodies are located mainly in the primary motor cortex. From there, the tract crosses entirely from one side of the brain to the opposite side of the body in the medulla. Thus, damage to cell bodies of this tract (which are in motor cortex) results in deficits in movement on the opposite side of the body. This tract is responsible for the fine movement of distal (i.e., far) limb muscles, such as those that move the arms, hands, fingers, lower leg, and foot. Damage to the [lateral corticospinal tract](#) has profound effects on the ability to reach, grasp, and manipulate objects.

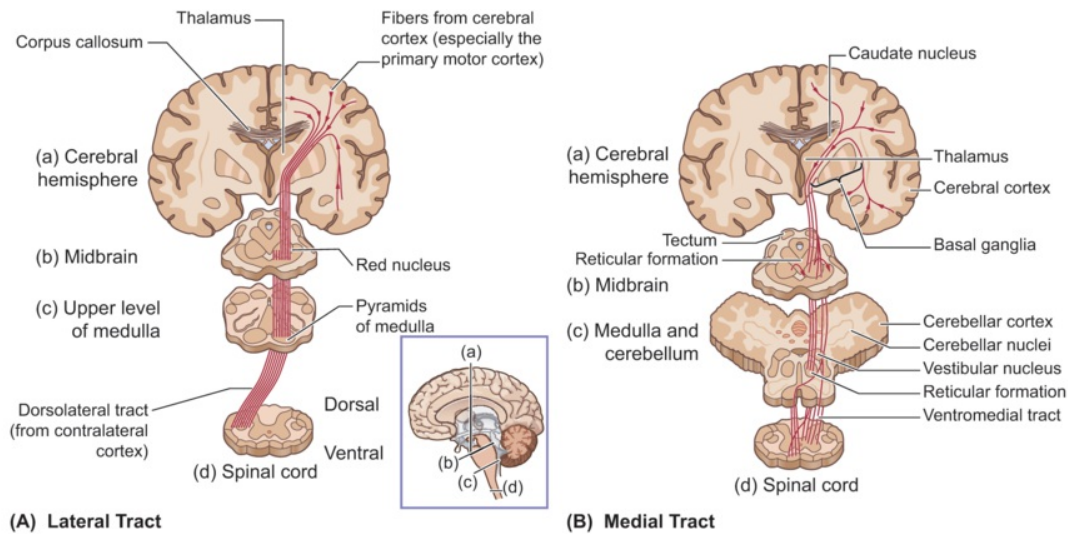


Figure 4.3 The two major motor pathways from brain to muscle.

(A) The lateral tract crosses from one side of the brain to the opposite side of the spinal cord and controls precise movement in the extremities, such as hand, fingers, and feet. (B) The medial tract produces bilateral control of trunk muscles for postural adjustments and bilateral movements such as standing, bending, turning, and walking. Inset shows location of cuts a, b, c, and d.

The other main pathway, the [medial pathway](#), is more involved in control of movements of the trunk and proximal (i.e., near) limb muscles. It projects both contralaterally and ipsilaterally, and is mainly involved in the control of posture, as well as bilateral movements such as standing, bending, turning, and walking. Now that we know how information gets from the brain to the muscles, let's examine the roles that different brain regions play in controlling movement.

Brain Structures Involved in Motor Control

As we mentioned, many brain regions are involved in motor control. In this section, we review the primary brain structures involved in such motor control, starting with those located outside the cortex and then discussing those in the cortex.

Subcortical Regions

Cerebellum

Looking like a small cauliflower attached to the back of the brain, the [cerebellum](#) plays an extremely important role in motor control, especially in the coordination of muscle movement timing, the planning of movements, and the learning of motor skills.

The cerebellum is organized into three main divisions. These divisions each receive a distinctive type of information and then in turn send their output to distinct portions of the nervous system. As such, it should not be surprising that each division of the cerebellum plays a somewhat distinct role in motor control (see [Figure 4.4](#)).

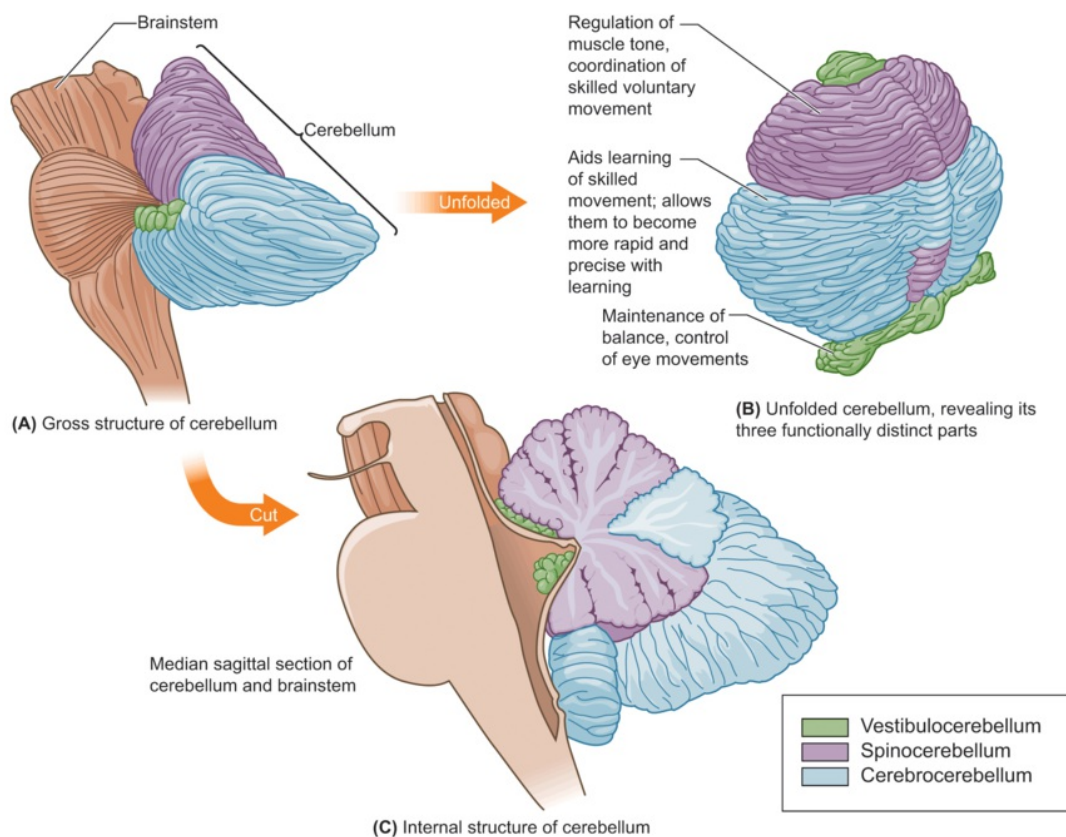


Figure 4.4 Structure of the cerebellum showing its inputs and outputs.

The three main divisions of the cerebellum: vestibulocerebellum, spinocerebellum, and cerebrocerebellum.

The vestibulocerebellum is the phylogenetically oldest part of the cerebellum. As the name implies, this region receives input from the vestibular nuclei in the brainstem

and then projects back to this region. Not surprisingly, then, damage to this region leads to difficulty with balance and to postural instability.

The spinocerebellum, located in medial regions of the cerebellar hemispheres, receives somatosensory and kinesthetic information (which is information about body movement derived from the muscles, skin, and joints) from the spinal cord and projects back to the spinal cord. Damage to this region results in difficulty with the smooth control of movement. More medial areas are involved in movement of proximal muscles, such as coordinating the trunk and leg muscles for walking (for review, see Morton and Bastian, [2004](#)). When people with damage to this region walk, their steps are often short and irregular, and their movements are erratic. More lateral areas are involved in moving more distal muscles, such as the arm muscles. The ability to position the arms, as well as the regulation of agonist and antagonistic muscles in sequence, is disrupted when this region is damaged.

The cerebrocerebellum receives input from many different regions of the cortex, including both motor and association cortices. This region is involved in the regulation of highly skilled movement that requires complex spatial and temporal sequences involving sensorimotor learning. These activities include motor abilities such as throwing a pitch, serving a tennis ball, and juggling, as well as fluent writing and speaking.

A few general principles about the cerebellum are worth noting. First, the projection of information through these cerebellar loops makes the cerebellum perfectly positioned to have a modulating effect on motor processing. Underscoring this point, the effects of cerebellar damage do not eradicate movements; rather, they degrade motor capabilities. Second, unlike the motor cortex, which acts on contralateral muscles, the cerebellum modulates ipsilateral muscles. Finally, areas of the cerebellum near the midline tend to be responsible for functions associated with the body's center, including posture. In contrast, more lateral areas of the cerebellum control the lateralized structures, including the limbs.

Now let's look in a bit more detail at the type of difficulties observed after

cerebellar damage. In general, the difficulty in coordinating movement that is observed after cerebellar damage is called [cerebellar ataxia](#). However, when it involves speech output it is called [dysarthria](#). Dysarthria is characterized by speech that can be slow, monotonous, slurred, and indistinct with sometimes explosive and jerky variations in voice intensity (Spencer and Slocomb, [2007](#)). Speech, in fact, is highly demanding of muscle coordination, estimated to entail the coordination of 1,400 motor commands per second (Lenneberg, [1967](#))!

As mentioned in [Chapter 1](#), neurologists often screen for cerebellar damage by having the patient touch his or her nose and then the neurologist's finger. A person with damage to the cerebellum can perform this task, but the path the hand takes from the nose to the doctor's finger is often staggered, jerky, and zigzag, especially as he or she zeroes in on the target. This behavior is sometimes referred to as an [action tremor](#) or [intention tremor](#) because it occurs during the performance of an act. This type of tremor is distinct from tremors seen with disorders of the basal ganglia, in which the tremor is much more likely to occur at rest. Moreover, in cerebellar ataxia, the patient often overshoots the target. This overshooting is an example of their struggle to calculate when each of the agonist and antagonist muscle groups must be turned on and then off to land at the target (see [Figure 4.5](#) for an example of these two symptoms).

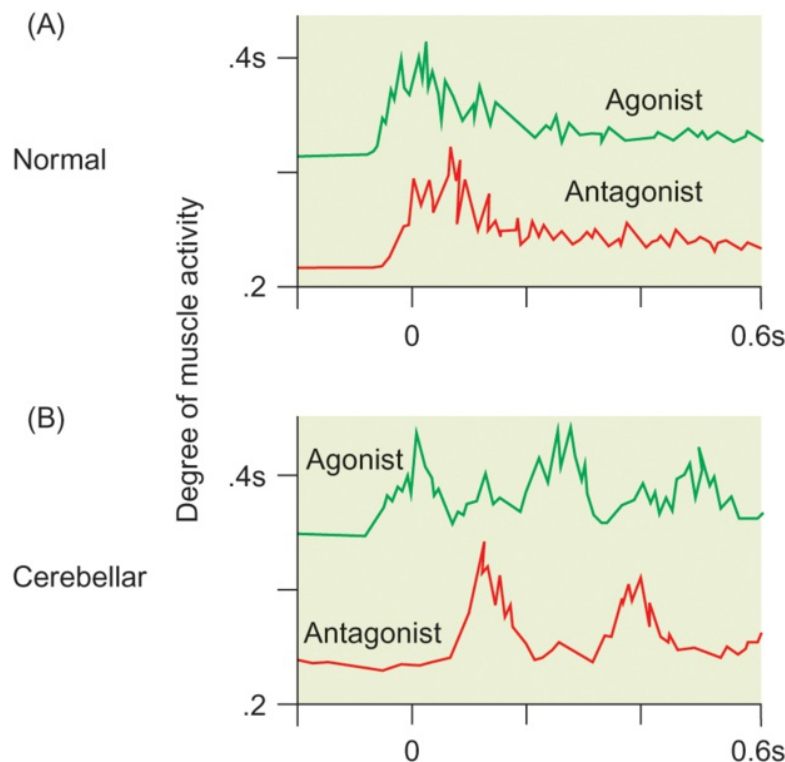


Figure 4.5 The mechanics that produce overshoot in patients with cerebellar damage.

Shown here is the activity of agonist and antagonist muscles in a single-joint motion from a hand (A) unaffected by cerebellar damage and (B) affected by cerebellar damage. Time is depicted along the x axis and degree of muscle activity along the y axis. Note that for the normal hand, the activity of the antagonist muscle (shown in red) lags slightly behind that of the agonist and also is similar in size, acting as an effective brake on movement as shown by the reduced amplitude of activity for both sets of muscles after about .2 seconds. In contrast, for the affected hand, the antagonist muscle activity comes too late and also too strongly. This induces more activity in the agonist, which then is poorly modulated by the antagonist, leading to overshoot of the target. This back and forth pattern between agonist and antagonist muscles leads to continued activity, which manifests as tremor.

Another set of difficulties exhibited by people with cerebellar damage is the coordination of multijoint movements (Thach, [2014](#)). Because multijoint coordination breaks down, movements are best accomplished by moving one joint at a time in a serial manner, a strategy known as [decomposition of movement](#). For example, rather

than lifting a glass by moving the entire arm, a person with damage to the lateral cerebellar cortex may place an elbow on a table, lean forward, and bring the glass to his or her mouth. With the elbow stationary, the number of joints that must be moved is decreased, which increases the likelihood of a successful movement (Bastian et al., [1996](#)). These difficulties reflect an inability to correctly control the muscles that rotate the joints but also to predict and compensate for the dynamic interactions of the distinct rotations of different joints.

Damage to the cerebellum can also hamper the learning of new movements (e.g., Deuschl et al., [1996](#)). Let's consider the case of throwing a dart at a target. The ability to coordinate eye fixation on a target with arm movement is an acquired skill. An individual with cerebellar damage who had decent eye-hand coordination prior to injury can throw a dart with relative accuracy, but if this task is changed a bit so it requires new sensorimotor learning, deficits appear. For example, if a person is wearing prism eyeglasses that displace the view of the world 15 degrees to one side, hitting the target will require a recalibration of the relationship between the position of the gaze and the arm movement. With practice, neurologically intact individuals can gradually make this adjustment, whereas patients with cerebellar damage cannot ([Figure 4.6](#)).

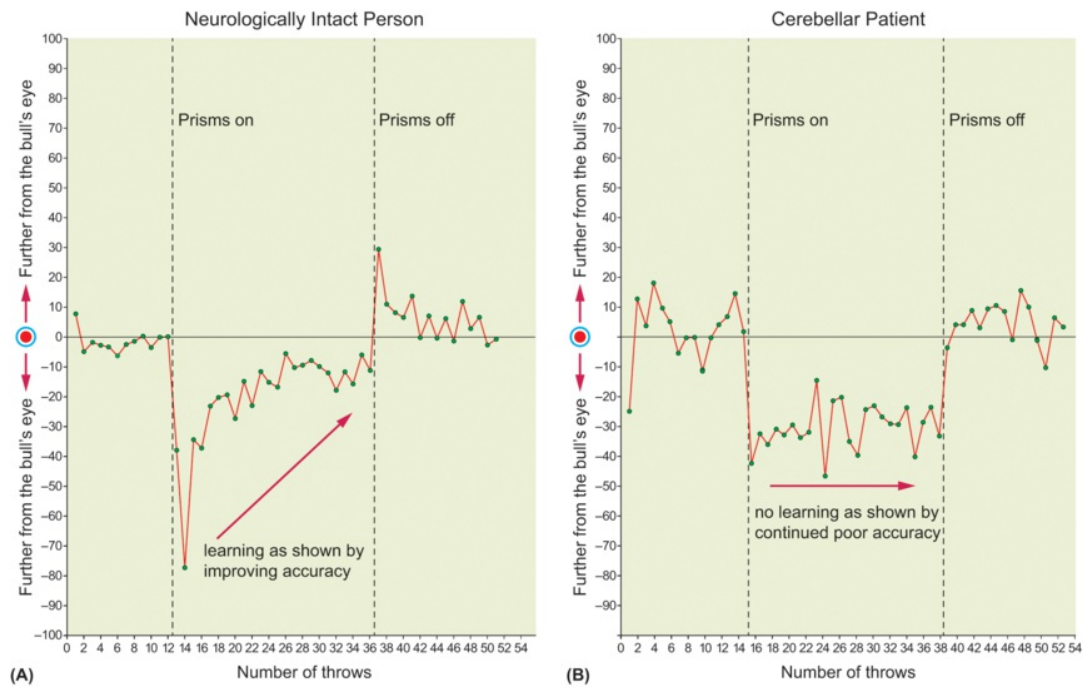


Figure 4.6 Role of the cerebellum in motor learning.

Shown here are plots of dart-throwing accuracy for a series of throws by two individuals. The first dashed line indicates when the individual puts on the prism spectacles, and the second dashed line when they are taken off. (A) Plot for a neurologically intact individual. After putting on the prisms, the person's throw is far off target, but with practice, the person's aim improves. After the eyeglasses are removed, the throw is off again but quickly becomes recalibrated. (B) Plot for an individual with cerebellar damage. The introduction of the eyeglasses leads to inaccurate throws, which are not adjusted with practice. Because no learning has taken place, the person's accuracy returns to the pre-prism baseline almost immediately after the eyeglasses are removed.

Finally, the lateral portion of the cerebellum may be important in sensorimotor learning and skills that require such learning. Eye-blink conditioning is a classic example of the role of the cerebellum in such learning (Gerwig et al., [2007](#)). In this paradigm, an animal (or person) hears a tone, which then predicts that a puff of air will be delivered to the eye. Blinking the eyes reduces the aversive effects of the air puff, but only if the timing of the blink relative to the tone is appropriate. It is well known that damage to the cerebellum interferes with the ability to learn to make an anticipatory

response at the correct time interval and interferes with the response after it has been learned.

Given these findings, it has been suggested that the cerebellum plays a critical role in sensorimotor learning because it promotes understanding of the nature of the temporal relationship between events. Supporting this idea, neuroimaging studies have demonstrated that as the temporal lag between hand and eye movements increases, making hand-eye coordination more difficult, the involvement of the cerebellum in task performance also increases (Miall et al., [2001](#)).

How are we to integrate all these diverse symptoms into a unified understanding of cerebellar function? There are a few different theories, which we describe briefly here. One prominent theory argues that the cerebellum helps to predict the sensory consequences of motor plans (Ito, [2008](#)). This is often referred to as a **forward model** (because you are predicting what will happen in the future, which is forward in time). That prediction can be used to determine if the sensory feedback is indeed consistent with the motion that is being performed (e.g., my sensory experience is what I anticipated). For example, if you decide to pick up a full carton of milk from a table, you have – in advance – a model of how that should feel and how much force you will need to pick it up.

Recently, it has been suggested that the cerebellum may also play such a role with regards to the internal planning of thought. More specifically, the cerebellum may help create motor plans, especially those related to inner speech, that can be used to support working memory and guide behavior (Marvel and Desmond, [2010](#)). For example, the cerebellum may help support the planning of the speech phrase, “And after I add the flour, I need to beat the batter for 30 seconds,” which may aid in the cognitive processes required to complete a recipe.

Relatedly, having such a model can help the brain to “subtract out” any sensory feedback that is irrelevant to task performance. Have you ever noticed that it is nearly impossible to tickle yourself? Because you already know what the sensory

consequences of tickling yourself would be, you are relatively impervious to the results of your motor action. In fact, there is less cerebellar activity in response to a self-produced tactile stimulus than to one that is externally generated (Blakemore et al., [1998](#)).

Importantly, this forward model of the cerebellum is not influenced by feedback from the periphery, such as sensory and kinesthetic information. Once the movement has started, the cerebellum is not involved in on-line adjustment of the movement. This makes the cerebellum particularly important for ballistic movements, which occur rapidly over a short period of time with maximal velocity and acceleration, leaving little or no opportunity for on-line modification. Rather, when movements require on-line adjustments, the parietal lobe plays a more prominent role, as discussed later in this chapter. It is thought that the cerebellum computes an error signal between how well it predicted the movement and the end result of the movement. This error signal then provides information on how the predictive model should be changed or updated for the next action (Bastian, [2006](#)).

A karate punch is an example of a ballistic movement – quick, rapid, and with little opportunity for on-line adjustment. The effectiveness of such punches is linked to the precision of the timing of the movements and is not governed by muscular strength (Voigt and Klausen, [1990](#)). In fact, studies examining the brains of black belts in karate find that their ability to control the timing of upper-body limb and joint movements is superior to novices, and that this ability is linked to the characteristics of the white-matter tracts that connect the cerebellum to the midbrain (Roberts et al., [2013](#)).

What is observed in patients with cerebellar damage and in neuroimaging studies is consistent with the idea that the cerebellum creates a forward model. For example, in the prism study, patients are unable to use the information about the accuracy of their aim (how far the dart was from hitting the target) to adjust their model of what movement would be needed on the next throw to land the dart closer to the target. In neurologically intact individuals who have learned a task involving hand-eye coordination, cerebellum activation varies depending on whether the hand was leading

the eye, or the eye was leading the hand, suggesting that the cerebellum was predicting the state of one effector (e.g., the hand) to lead the other (e.g., the eyes) (Miall and Jenkinson, [2005](#)).

A different idea is that the cerebellum is a timing device that provides a clock for events. According to this idea it provides information on the timing for the initiation and cessation of movement for different effectors (e.g., arms, hands) (Ivry and Spencer, [2004](#)). For example, lesions to the cerebellum compromise the ability to perform simple but precisely timed tapping movements, and the cerebellum has been implicated in control of the correct pronunciation of syllable strings, based on what syllable will precede or follow a particular utterance (Ackermann et al., [2007](#)). Such a timing mechanism may be used for a variety of mental processes as well, providing information on event timing in which temporal goals are explicitly represented (Ivry et al., [2002](#)).

Evidence for the broader role of the cerebellum in timing comes from studies in which cerebellar lesions impair the ability to make judgments about the temporal duration of events, such as whether the time gap between the presentation of two tones is longer or shorter than a reference interval (e.g., 400 ms) or which of two successive displays of dots is moving more quickly across the screen. Recently it has been suggested that the cerebellum is mainly involved in the timing of discrete intervals that are not continuous or dynamic in nature. For example, patients with cerebellar damage are not impaired in drawing a circle, which requires continuous movement (Breska and Ivry, [2016](#)).

If such a timing mechanism is disrupted, it would explain not only why the initiation and cessation of different muscle groups' action cannot be well coordinated after cerebellar damage, but also that neuroimaging studies reveal activation of the cerebellum (particularly in lateral regions) during higher-level cognitive tasks (Stoodley and Schmahmann, [2009](#)). A role for the cerebellum in timing is also consistent with changes in cerebellar anatomy and function that have been noted in a number of developmental (Stoodley, [2016](#)) and psychiatric disorders (Bernard and

Mittal, [2015](#); Shakiba, [2014](#)), such as autism, dyslexia, attention-deficit/hyperactivity disorder, and schizophrenia (all of which are discussed in later chapters), the symptoms of which are not mainly motoric in nature.

Regardless of which of these theories – the forward model or the timing theory– ultimately turns out to be a better description of cerebellar function, they highlight the role played by the cerebellum in the coordination, learning, and timing of movements (see Mauk et al., [2000](#), for further discussion).

Basal Ganglia

The [basal ganglia](#) are a complex collection of subcortical nuclei, consisting of the [caudate nucleus](#), [putamen](#), and [nucleus accumbens](#) (known collectively as the striatum), the [globus pallidus](#) (or pallidum), the [substantia nigra](#), and the [subthalamic nucleus](#). The position of the basal ganglia within the brain is shown in [Figure 4.7](#).

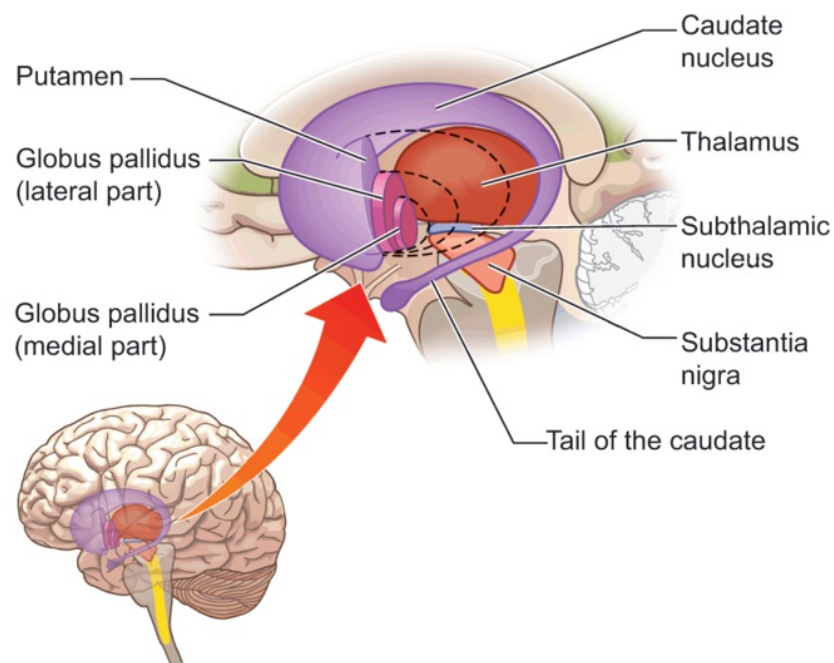


Figure 4.7 Basal ganglia in relation to other brain structures.

The basal ganglia surround the thalamus and in turn are surrounded by the cerebral cortex.

Like the cerebellum, the basal ganglia are in a position to modify movement because they form a series of somewhat separable loops with cortical regions. The basal ganglia receive input from cortical regions, with distinct cortical regions projecting to different regions of the caudate and putamen. Output from the basal ganglia occurs via the globus pallidus to the thalamus, which then projects back to the cortex. Each loop consists of input from a cortical region to which information then returns (see [Figure 4.8](#) for a diagram of these connections). Four such loops have been identified: a limbic (emotional) circuit, an associative (cognitive) circuit, a sensory circuit, and a motor circuit (Redgrave et al., [2010](#)).

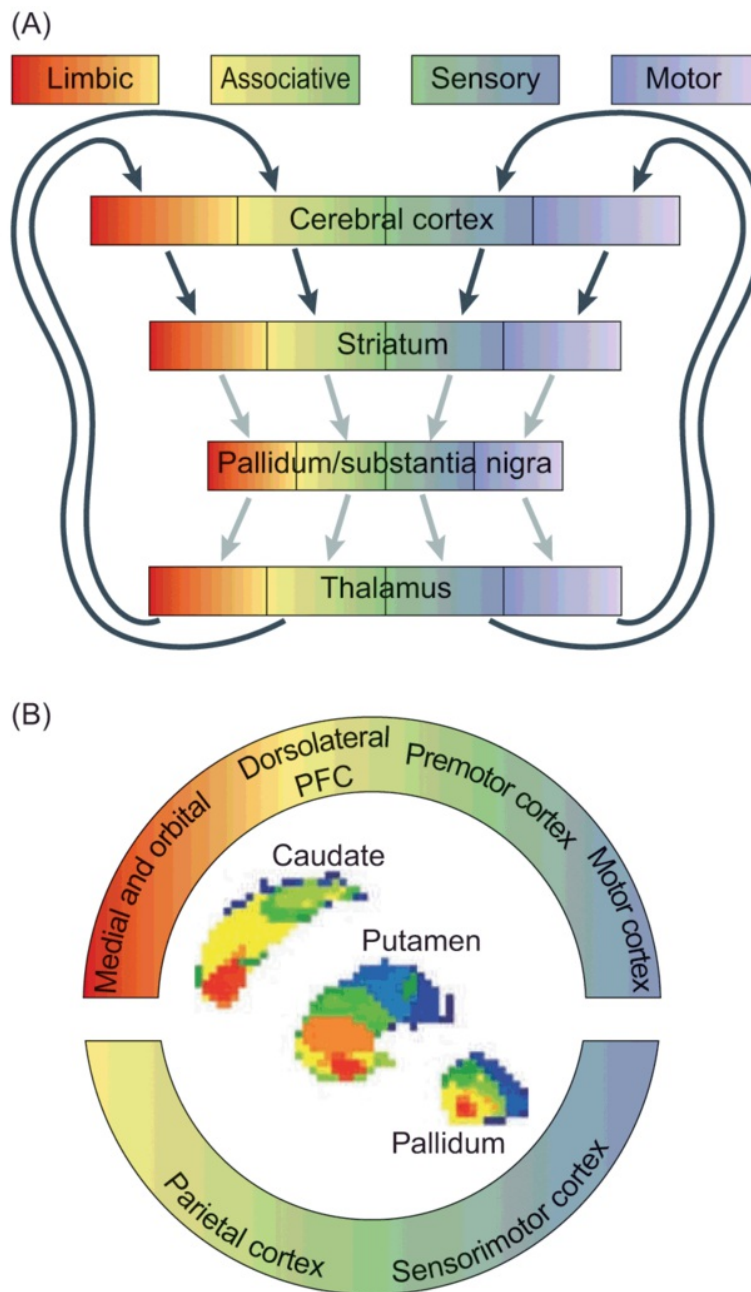


Figure 4.8 The parallel loops between the basal ganglia, thalamus, and cortex.

(A). Shown here are the four major loops, each serving a different function. Each loop is denoted by a distinct color: red for the limbic loop, yellow for the associative loop, green for the sensory loop, and blue for the motor loop. The colors are shaded because these loops are not totally distinct with some overlap and interaction between them. Glutamatergic projections are shown in black while GABAergic projections are shown in gray. (B) Spatial topography of the four major loops. Notice that the loops are organized in an anterior to posterior direction. The limbic loop

occupies the most anterior portions of the striatum (caudate and putamen) and the pallidum and connects to medial and orbitofrontal prefrontal cortex. Next are the associative loops which connect to dorsolateral prefrontal and parietal cortex. Following that is the sensory loop that connects to sensorimotor and premotor cortex, followed by the motor loop which connects mainly to motor cortex.

(from Redgrave et al., [2010](#))

Besides these loops, the basal ganglia have additional inputs (substantia nigra to the striatum via the nigrostriatal bundle; subthalamic nucleus to the globus pallidus) and outputs (basal ganglia to the superior colliculus for influencing eye movements). As a result, the basal ganglia, thus, are at the crossroads of the neural circuits involved in motor control, which positions them perfectly to modulate motor activity (Middleton and Strick, [2000](#)).

The basal ganglia are important for the accomplishment of movements that may take some time to initiate or stop, unlike the cerebellum, which plays a role in movements that are not modified once they have been initiated. The basal ganglia are thought to have multiple roles in motor action themselves: “setting” the motor system with regard to posture; preparing the nervous system to accomplish a voluntary motor act; acting as an autopilot for well-learned sequential movements; and controlling the timing of and switching between motor acts. Because they receive both motor and nonmotor information, the basal ganglia are also thought to assist in motor planning and learning, especially when motor acts have motivational significance (i.e., lead to a reward) or have a large cognitive contribution (i.e., learning new input-output rules that override well-learned behavior; see Graybiel et al., [1994](#)).

How can these diverse activities be grouped in a meaningful way to understand the role of the basal ganglia in motor control? A variety of different viewpoints have been provided. One overarching theory of basal ganglia function suggests that the basal ganglia facilitate the synchronization of cortical activity underlying the selection of appropriate series of movements while inhibiting inappropriate ones (Mink, [1996](#)). For

example, it can help in selecting the action of raising your arm as you hit a tennis ball, but not raising your head so as to keep your eyes on the ball. Another theory states that the basal ganglia “chunk” individual actions into coordinated, stereotyped, and habitual units of action (Graybiel and Grafton, [2015](#)). For example, as you learn a tennis serve, the basal ganglia help to chunk the requisite steps – tossing the ball, dipping your legs, bringing the racquet behind your back, and so forth – into one unit of action. Another theory suggests that they aid the ability to execute movements with varying vigor, that is, over a range of speeds, amplitudes, and frequencies (Dudman and Krakauer, [2016](#)). From this viewpoint, the basal ganglia help you adjust your tennis serve depending on whether you want to produce a faster and stronger serve that after landing bounces straight back at the opponent, as compared to a trickier “spin” serve that arrives more slowly and weakly, but then after landing “kicks away” from your opponent. Relatedly, the degree of vigor may be linked to motivational factors (Turner and Desmurget, [2010](#)), such as whether a motor action led to a reward or not, and how much effort you wish to put into your actions. For example, if despite your best efforts, your opponent is winning all the points on your good fast serve, your basal ganglia may help you adjust to a slow, weaker serve, in the hopes that it will throw your opponent off so you can be rewarded and win more points, and that it will reduce your effort and conserve your energy to, as they say, “fight another day.”

Regardless of which of these theories proves to be the best description, the anatomy of the basal ganglia provides them with the ability to both facilitate action and also to inhibit it. To better understand the role of the basal ganglia in movement and movement disorders, look at [Figure 4.9](#), which illustrates the central aspects of basal ganglia anatomy and function (Utter and Basso, [2008](#)). There are two routes via which information passes through the basal ganglia. One route, the direct route, contributes to sustaining or facilitating ongoing action. In this route, input to the basal ganglia occurs via inputs that synapse on D₁ receptors of medium spiny neurons of the caudate and putamen. When excited these neurons release GABA, and as such directly inhibit the

internal section of the globus pallidus on which they synapse. The internal section of the globus pallidus then in turn has inhibitory connections to motor nuclei of the thalamus, which in turn has excitatory connections with the cortex. As a result, activity in the direct route normally causes inhibition of the internal sections of the globus pallidus so that it can no longer inhibit the thalamus from exciting the cortex (a double negative). Therefore, activity in this route contributes to sustaining or facilitating ongoing action because inhibition of the thalamus is decreased.

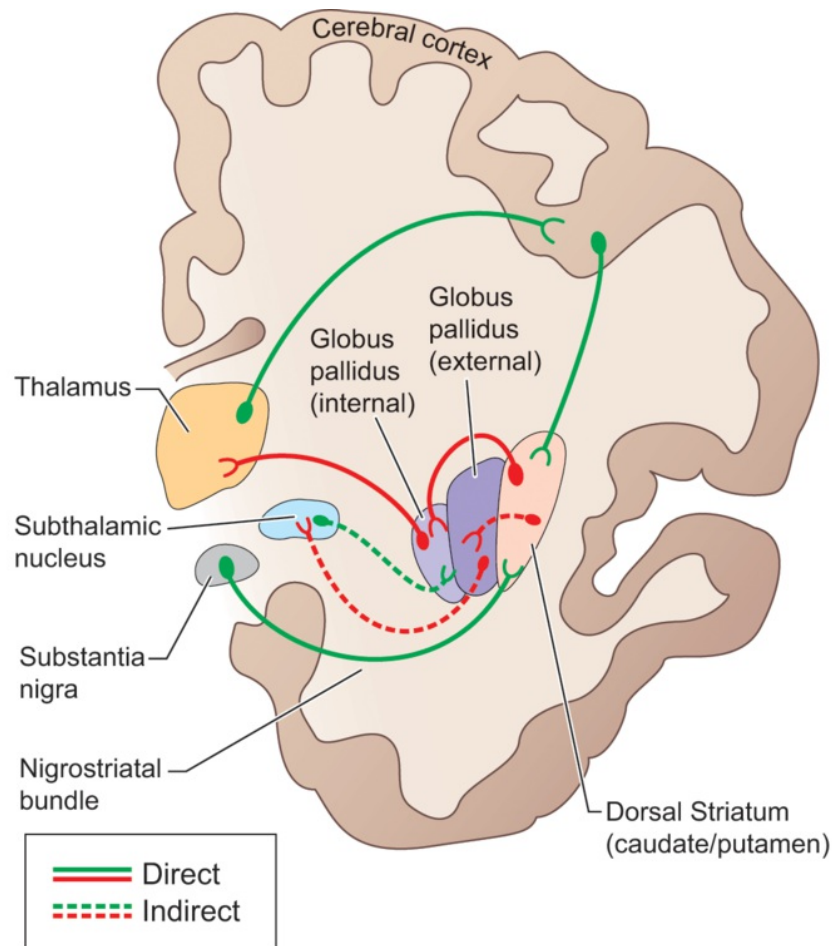


Figure 4.9 Connections between different sections of the basal ganglia.

Inhibitory connections are shown in red and excitatory connections are shown in green. Two routes exist between the caudate and putamen (which receive all the input to the basal ganglia) and the internal section of the globus pallidus (the main output region of the basal ganglia). One route is a direct route (inhibitory) between these two regions. The other is an indirect route from the caudate and putamen to the external section of the globus pallidus (inhibitory), to the subthalamic nucleus (inhibitory), then finally to the internal section of the globus pallidus (excitatory). The globus pallidus has inhibitory connections to motor nuclei of the thalamus. The motor nuclei of the thalamus excite the cortex.

(from Calabresi et al., [2014](#))

The other route, the indirect route, is thought to be important for suppressing unwanted movement. In this route, input to the basal ganglia occurs via inputs that

synapse on D₂ (rather than D₁) receptors of medium spiny neurons of the caudate and putamen. These neurons also release GABA but they synapse on and therefore inhibit the external (rather than the internal) section of the globus pallidus. This region has inhibitory connections to the subthalamic nucleus, which in turn has excitatory connections to the internal section of the globus pallidus. Thus, normal activity in the indirect pathway causes the subthalamic nuclei to activate the internal section of the globus pallidus, which suppresses thalamic activity, and keeps it from exciting the cortex. Classically these two pathways have been considered to work in opposition to one another, much the way the gas pedal and brake on a car have opposite effects and are independent of one another. However, newer research suggests there is more ongoing interaction between them in the selection and patterning of motor behaviors than previously thought (Calabresi et al., [2014](#)).

Damage to the basal ganglia produces distinct motor disorders, and can be better understood by knowing which regions of the basal ganglia are affected. Parkinson's disease is characterized by [akinesia](#) (the inability to initiate spontaneous movement), [bradykinesia](#) (slowness of movement), and [tremors](#) (rhythmic, oscillating movements). Notice that these symptoms are generally characterized by a reduction of movement. Given what you have just learned, these symptoms should suggest to you that perhaps some portion of the direct route, which facilitates movement, is disrupted. Indeed, classic models of Parkinson's disease argue that the direct pathway is compromised because the putamen is not receiving adequate input. In Parkinson's disease, the cell bodies in the substantia nigra, which provide input to the basal ganglia through the nigrostriatal bundle, have died. The death of cells in the substantia nigra (meaning "black substance") can be seen easily on autopsies of patients with Parkinson's disease, because this region does not stain the usual dark color seen in neurologically intact individuals. Because there is very little input to the direct pathway from the substantia nigra, the indirect pathway becomes overactive (refer back to [Figure 4.9](#)), causing much

activity in the internal portion of the globus pallidus, which in turn inhibits the thalamus and results in decreased motor activity (Albin et al., [1989](#)).

Individuals with Huntington's disease, another disease that affects the basal ganglia, exhibit quite different symptoms, with [hyperkinesias](#) (involuntary, undesired movements) being quite common. One type of hyperkinesia is [chorea](#) (derived from the Greek khoros, meaning "dance"), which produces uncontrollable, jerky movements such as twitching and abrupt jerking of the body. Another type is [athetosis](#), characterized by involuntary writhing contractions and twisting of the body into abnormal postures. This set of symptoms should suggest to you involvement of the indirect pathway, which as we just learned is important for the inhibition of movement. In Huntington's disease, there is a selective loss of striatal neurons that bind gamma-aminobutyric acid (GABA). These neurons give rise to the indirect pathway from the striatum to the globus pallidus, leading to underactivity in this pathway. More specifically, the loss of inhibitory input to the external globus pallidus causes it to become more active. As a result, there is increased inhibition of the subthalamic nucleus. As a result of this increased inhibition, the subthalamic nucleus does not excite the internal section of the globus pallidus, reducing the output from the globus pallidus. This decreased output in turn lessens inhibition of the thalamus, which in turn leads to more motor activity in the cortex (refer back to [Figure 4.9](#); Albin et al., [1989](#)).

Later in this chapter we discuss both Parkinson's and Huntington's disease in more detail, focusing on the motoric aspects of these disorders. As mentioned above, however, the basal ganglia are also thought to be important for habit learning, in which specific environmental conditions or inputs trigger a relatively automatic motor response. Moreover, the basal ganglia may help to signal when the environmental conditions have changed such that a different response, idea, or thought should be given prominence (Frank et al., [2001](#)). Thus it should not surprise you that individuals with Huntington's and Parkinson's exhibit difficulties in some aspects of cognitive

functioning along with their difficulties in motor control. We save the discussion of the cognitive difficulties associated with these disorders for [Chapter 16](#).

Cortical Regions

In contrast to the cerebellum and basal ganglia, which are important for modulating movements, the major role of cortical regions in motor control is in planning and guiding skilled movements and those that require linking sensory inputs with motor outputs. Cortical regions support a range of motor abilities, including picking up an object, using a tool, producing a gesture in response to a verbal command, moving the eyes to explore the image of a face, and controlling the body as we move around the environment. As befits this long list of abilities, quite a number of different cortical regions play a role involved in motor control. Before we describe each of these areas in more detail, we first need to become familiar with their locations in the brain.

As shown in [Figure 4.10](#), cortical motor areas are distributed across the frontal lobe, located on both lateral and medial surfaces. We'll start with a description of the regions on the lateral surface. First, notice the location of the [primary motor cortex](#), directly in front of the central fissure. Although the majority of primary motor cortex is located on the lateral surface of the brain, it wraps from the dorsal section of the lateral surface down the horizontal fissure to the medial surface (where the representation of the leg and foot are located – refer back to [Figure 1.23](#)). Premotor cortex is directly in front of primary motor cortex on the lateral surface. Finally, the [frontal eye fields](#) (FEFs) are located at the ventral end of this region but above Broca's area (see Paus, [1996](#)).

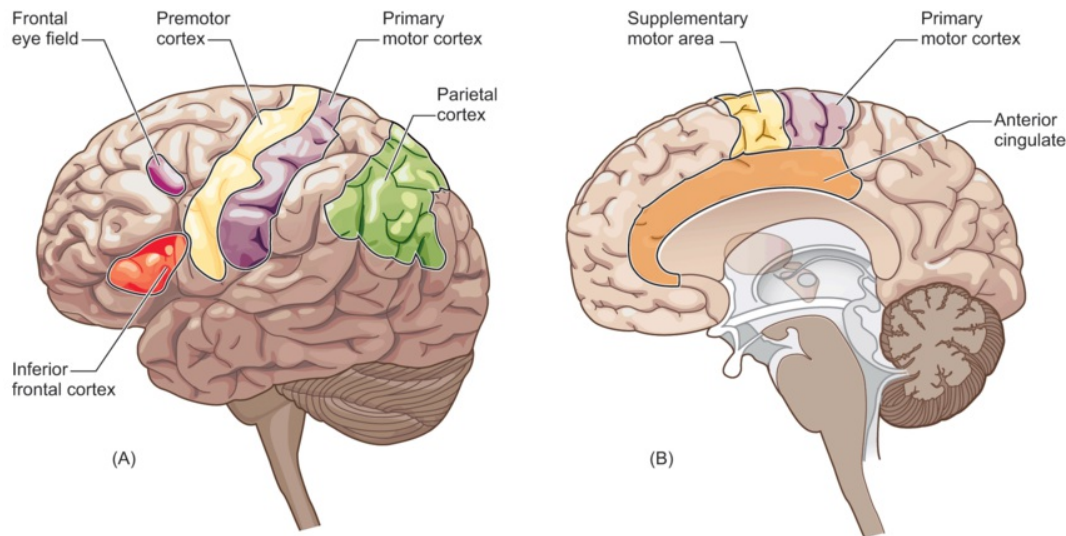


Figure 4.10 The major regions of the cortex involved in motor control.

(A) Left hemisphere, lateral view. (B) Right hemisphere, midsagittal view.

Now let's look at the medial surface. The [anterior cingulate cortex](#) is above the corpus callosum and below the cingulate sulcus, extending as far back as the central fissure. The [supplementary motor complex](#) (SMC) is above the cingulate cortex and in front of the primary motor region. One other portion of the brain that is involved in motor control, but not located within the frontal lobe, includes portions of the superior and inferior parietal lobes.

Each of these regions makes a different contribution to motor control, as we will see in detail in the following sections. Primary motor cortex controls the force and/or direction with which the motor plans are executed. Generally, the premotor region, supplementary motor complex, and frontal eye fields are involved in the specifying, preparing, and initiating of movement. The anterior cingulate is important for selecting among particular responses and monitoring whether the execution of those actions occurred appropriately. Finally, parietal regions are involved in linking movements to extrapersonal space and sensory information, as well as linking movements to meaning, as occurs in gesture. Through the multiplicity of roles of these regions and their coordination, the richness of our ability to act on the world is expressed.

Primary Motor Cortex

Primary motor cortex (sometimes referred to as M1) provides the command signal to drive motor neurons to make muscles move. When the primary motor cortex is damaged, the person cannot control the force with which muscles are exerted. In the most severe cases the result is hemiparesis, the inability to make motor movements on one side of the body, while in less severe cases, weakness and imprecise fine movements occur. As we learned in Chapter 1 (see [Figure 1.23](#)), motor cortex is organized so that different subregions of motor cortex control action of specific portions of the body, such as the fingers, arms, or legs. Thus, while neurons within each of these regions are responsible for control for a specific portion of the body, exactly how does activity across these neurons code for movement?

Scientists have discovered that movements are coded in the form of a neuronal population code, meaning the summed activity across the entire set of neurons within a specific subregion of M1 (e.g., the arm region) determines the direction of movement for that body part. While each neuron may be tuned to fire maximally to movement in a particular direction, the summed activity across the population of neurons determines the direction of the movement (see [Figure 4.11](#)). It is as if for every movement, each and every neuron votes, and the outcome of the vote determines the direction of movement. If the intended movement is in a neuron's preferred direction, it fires a lot and has a loud vote; if the movement is not in the direction preferred by the neuron, it fires less and has a quieter vote (Georgopoulos et al., [1986](#); Georgopoulos and Carpenter, [2015](#)). If a monkey has to rotate the direction of movement in a systematic, continuous manner (e.g., slowly turn 90 degrees clockwise), the activity of the population code shows a systematic change with that rotation (Georgopoulos et al., [1989](#)).

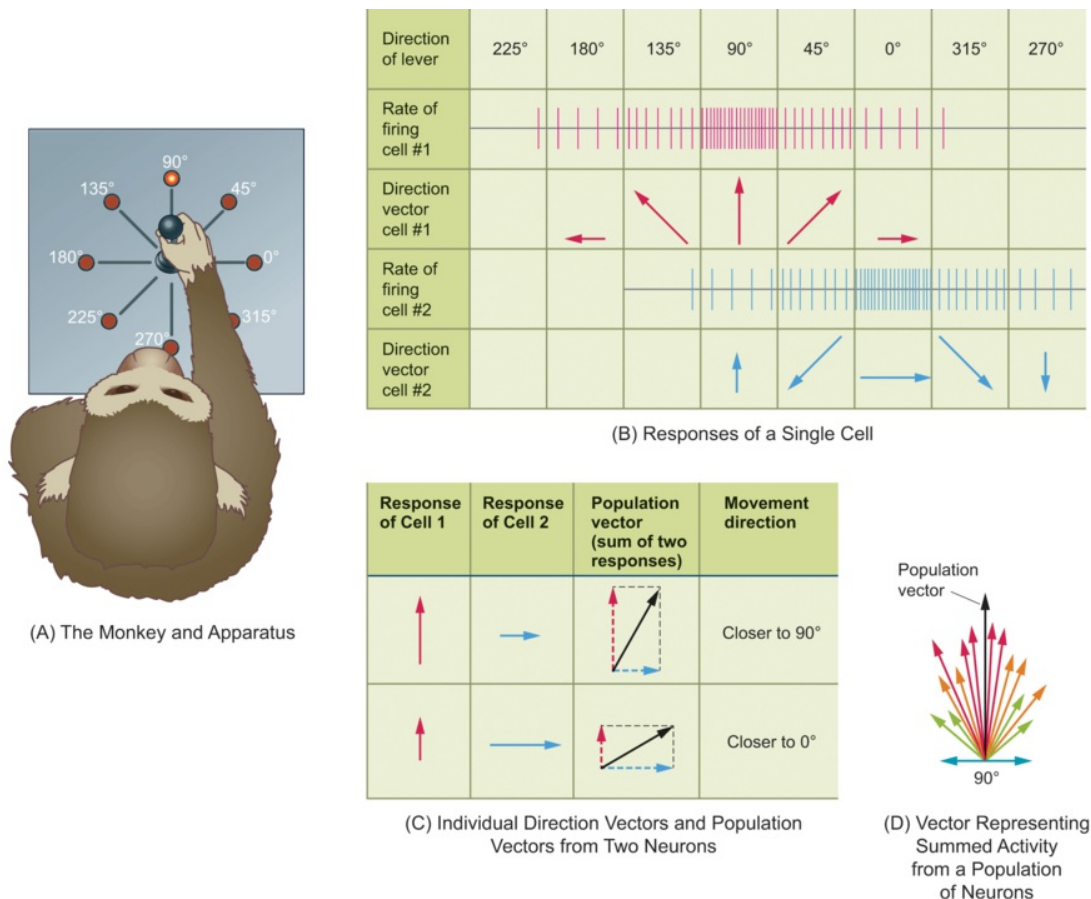


Figure 4.11 The direction of movement is encoded by populations of neurons.

(A) In single-cell recording studies, monkeys are trained to move a joystick in response to light in a specific location. (B) Shown here are two cells, one that is tuned maximally to movements at 90 degrees and another that is tuned maximally at 0 degrees, although both cells will respond to movements within approximately 45 degrees of their preferred direction. (C) Responses of single cells can be combined into population coding. Shown here is a simplistic example in which the direction of movement is determined by activity in just two cells. (D) In the motor cortex, it is the summed response across the population of neurons that accurately predicts the direction of the monkey's movement. In other words, the population of cells essentially tallies up individual cell "votes" regarding the best direction to move.

While we know that the population code controls the direction of movement, exactly what is the activity of neurons telling the muscles to do? Scientists have assumed that at the most basic level, neurons in M1 code for the force with which a movement is made

(Scott, [2000](#)) – more activity, more force. Yet, other findings tell us that this can't be the whole story (see Scott, [2008](#), for a longer discussion). For example, when a constant load is applied to certain muscles, the activity across the population of neurons can vary depending on whether the monkey is maintaining a posture or is reaching (Kurtzer et al., [2005](#)). And M1 cells are also sensitive to torque (rotational force) of joint acceleration, and to overall trajectory and distance to target, among other things. The exact computation that is being performed by M1 cells remains to be determined.

Recent research also suggests that the classical conception of the organization of the motor cortex may have to be revisited. Short-duration stimulation of motor cortex leads to movement of particular body parts depending on the regions stimulated, as we have discussed both above and in [Chapter 1](#). Longer trains of stimulation (on the order of 500 ms or longer), however, result in more complex coordinated movements that are of critical importance for the animal, including hand-to-mouth movements, reaching motions, and motions to protect the body from attack (see [Figure 4.12](#)). Therefore, some researchers have suggested that motor cortex may be organized for ethologically relevant behaviors, rather than on the basis of specific body parts per se (Graziano, [2016](#)).

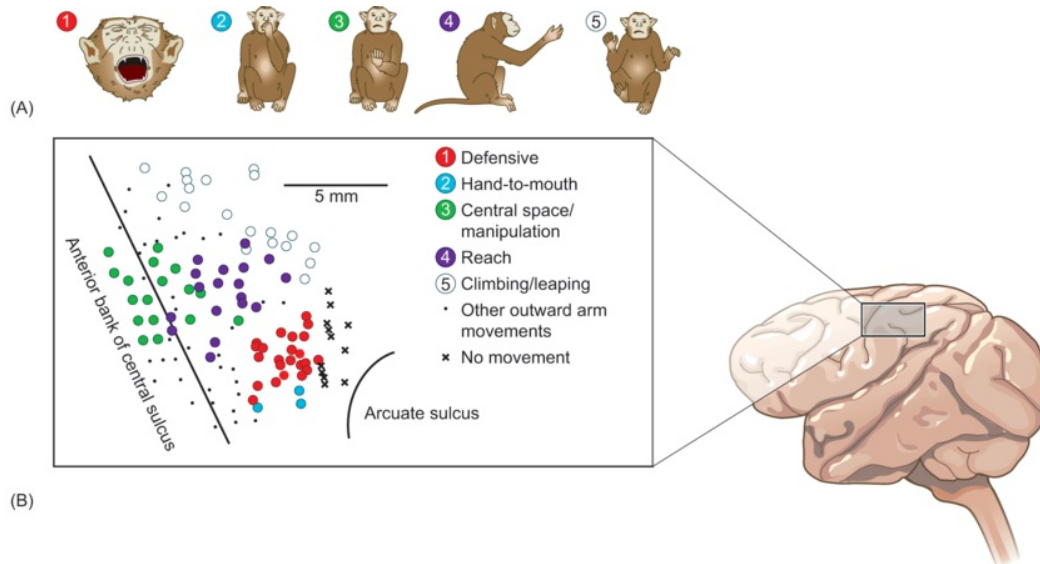


Figure 4.12 The organization of motor cortex for ethologically relevant behaviors.

(A) Five types of movement that are elicited by stimulation of primary motor regions: (1) defensive-like posture of the face; (2) hand-to-mouth movements; (3) manipulation-like shaping of the fingers (precision grip) and movement of the hands to central space; (4) outward reach with the hand opened to allow for grasping; and 5) climbing or leaping-like posture of all four limbs. (B) A map of the regions of motor cortex that elicit these movements when stimulated: (Left) Circle and symbols represent areas of stimulation, with color and shape indicating the type of movements elicited by stimulation at that site. Notice the systematic topography with similar motions occurring within distinct subregions. (Right) The gray square on the cortex indicates the region of the motor cortex that is shown in the square to the left.

In addition, control of movement by primary motor cortex may also be more flexible than previously thought. For example, in adults, learning a new motor skill can change the size of the cortical regions in primary motor cortex that represent each finger (e.g., Karni et al., [1995](#), [1998](#)). The regions of cortex devoted to fingers that are often used will expand, whereas those controlling fingers that are used less often will retract. (We discuss this issue of changes in the neural substrates underlying mental function, known as plasticity, in more detail in [Chapter 15](#).) Thus, although the classical model of the organization and function of motor cortex that we presented in [Chapter 1](#) provided a

good heuristic, it is clear that the true story is a bit more complicated and not yet fully understood.

Supplementary Motor Complex and Premotor Areas

Of course, skilled movement requires more than being able to move the muscles: it also requires coordination and timing of muscle movements. For example, merely having the ability to move our muscles is clearly insufficient if we want to give a speech or play the piano. Such complicated motor tasks require a plan of action. Areas of the cortex distinct from primary motor cortex but connected to it are believed to be important for the creation of such plans. After first reviewing the concept of a motor plan, we examine the areas involved in creating such plans: the supplementary motor complex and premotor regions.

Concept of a Motor Plan

A plan of action, or [motor plan](#) as it is often called, is an abstract representation of intended movement. It must contain not only general information about the goal that a series of movements is intended to achieve, but also specific information about the neuromuscular control that will allow the goal to be reached. Suppose that the goal of the plan is to type the sentence, “The lazy white cat just languished in the sun as the bunny bolted across the yard.” In this case, the motor program should contain information about which fingers will move, the order in which they will move, the direction in which they will move, the timing between movements, and so forth.

Evidence that the human brain creates an overall plan for a series of complicated movements comes primarily from studies examining motor control in the oral and manual domains. One phenomenon suggestive of motor planning is [coarticulation](#), which refers to differences in how the vocal muscles produce sounds (most notably vowels) depending on what precedes or follows them. For example, the sound of the vowel “u” requires the lips to be rounded (unless you are a ventriloquist!). In contrast, consonants can be produced acceptably with or without lip rounding. Thus, if a series of

consonants precedes a vowel requiring lip rounding, the consonants will be produced with rounded lips. Look at yourself in the mirror as you say “construe.” Notice that your lips are rounded as you begin to say “str” of the second syllable. Now look in the mirror at the shape of your lips as you say “constrict.” When you said the “str” of this word, your lips were not rounded, because the vowel “i” did not require it.

This example indicates that some preplanning of speech must have occurred. The question that arises is how far in advance this preplanning occurs. Are motor commands generated in a chain-like manner, allowing movements to be planned only a couple of steps ahead rather than requiring the entire sequence to be planned before an action begins? Or is the entire utterance planned in advance?

The answer appears to be that people can indeed plan an entire motor sequence before initiating action. Researchers in one study (i.e., Sternberg et al., [1978](#)) told their participants to produce a fluent stream of words, but only after a signal indicated to do so. The utterances were well practiced so that the participants could produce them fluently. The critical variable in the study was how long it took a person to begin to say the utterance after the signal appeared. The researchers reasoned that if the motor plan were being continually created “on-line,” the number of words in an utterance would not influence how long a person took to start the utterance. The person would plan speech “on the fly,” keeping a step or two ahead of what he or she was actually saying. Such a strategy would be invoked in the same way regardless of whether an utterance consisted of three words or seven. However, if a motor plan of the entire utterance is created before the person begins to speak, the time to initiate speech would be related to the length of the utterance. Because short utterances would require little time to plan, the person would begin to speak these more quickly than a longer utterance, which would require more time to plan. Results indicated that the time it took to begin speaking increased linearly with the number of words in the utterance. The conclusion is that the brain generates an entire plan of action before movement commences rather than creating the plan as actions are being performed.

The regions of the brain that are involved in creating motor plans lie outside the primary motor cortex. As a brief overview, the supplementary motor complex (SMC) comes up with the motor plan at the most abstract level, that is, sequencing the critical pieces. The premotor areas then code for the types of actions that must occur to meet that motor plan, and primary motor regions execute the commands to move the muscles. For example, if you wanted to uncork a bottle of wine, the SMC would code for the motor sequence needed: to steady the bottle with one hand and to use the other hand to position the corkscrew above the bottle, for twisting the corkscrew into the cork, and then for pulling to retract it. Premotor areas would code for the fact that the bottle must be grasped in a certain way, and that the corkscrew must be twisted in a particular direction and manner. Finally, primary motor areas would code exactly how the muscles would be controlled to implement the required grasp on the bottle and the force or torque with which to execute the twisting of the corkscrew.

Evidence for such a hierarchical control of movement comes from studies that combine the anatomical precision of PET with the temporal precision of MEG (Pedersen et al., [1998](#)). Activity in the SMC is observed 100–300 ms before an action begins. Afterward, activity in the premotor cortex is observed from 100 ms prior to the onset of movement, whereas activity in the primary motor cortex begins at movement onset and continues for another 100 ms. We now examine the function of each of these regions in more detail.

Supplementary Motor Complex

One of the main regions of the brain that plays a role in planning, preparing, and initiating movements is the [supplementary motor complex \(SMC\)](#) (refer back to [Figure 4.10](#)). It is composed of three subregions – the more posteriorly located supplementary motor area (SMA), the more anteriorly located pre-SMA, and the supplementary eye field (SEF), sandwiched between them (see [Figure 4.13](#)). In general, the pre-SMA is involved in more complex motor planning than the SMA, such as when one must decide for oneself what action to take, rather than having an action triggered by

an external cue. In addition, the SEF appears to be involved in the planning of eye movement, whereas the SMA does so for other body parts. While researchers still continue to debate and discover differences between these subregions (Nachev et al., [2008](#)), here we will focus more generally on the functions of the entire region, the SMC.

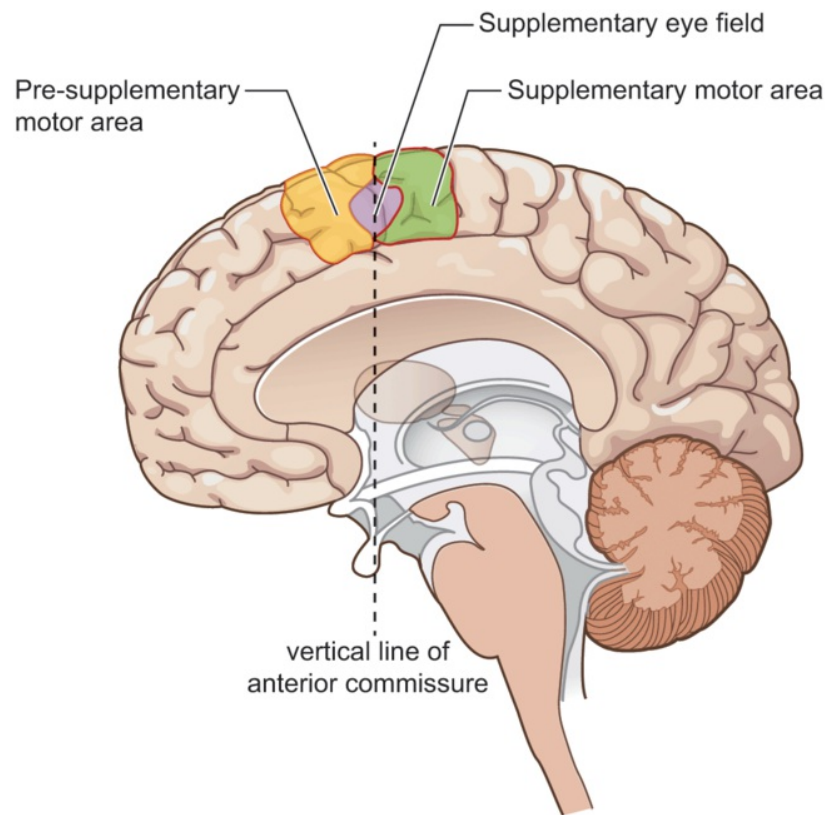


Figure 4.13 The brain regions that form the supplementary motor complex.

Shown here is the location, on the medial surface of the brain, of the supplementary motor area (SMA), the supplementary eye field, and the pre-SMA. The border between the pre-SMA and SMA is generally taken to be determined by a vertical line that extends from the top of the brain's surface to the anterior commissure, known as the vertical commissure anterior line or VCA line.

The SMC's role in motor planning has been demonstrated in studies with both animals and humans, which have shown that activity in this region precedes motor action. In monkeys trained to plan a simple response to a stimulus, the firing of SMC neurons (examined by using single-cell recording techniques) changed systematically when the movement was being planned. By comparing the time at which the firing rate

of a cell in the SMC changed with the time when electrical activity began in the limbs associated with the movement (remember, neuronal firing is necessary for a muscle to move), researchers determined that the firing rate in the SMC changed before electrical activity was recorded at the limb (Tanji et al., [1980](#)). The specific region of the SMA that becomes active depends on the limb that will be used, as it is organized somatotopically: stimulation of caudal sites causes activity in the hindlimb, whereas stimulation of the rostral sites, bordering the pre-SMA, causes movements of the forelimbs and orofacial region (e.g., Mitz and Wise, [1987](#)). And the SEF becomes active before movement of the eyes.

Other evidence suggests that the SMC plays an important role in planning the sequence and order in which actions occur. For example, particular neurons in the SMC will fire before a given sequence that starts with a particular action (say, a turn), but only when that action is followed by a specific sequence (say turn, pull, and then push a lever, but not turn-push-pull) (Shima and Tanji, [2000](#)) (see [Figure 4.14A](#)). Furthermore, some neurons in this area fire specifically to the position in a sequence in which an action occurs regardless of the nature of the actual action itself (e.g., a push, a pull, or a turn) (Clower and Alexander, [1998](#)) (see [Figure 4.14B](#)).

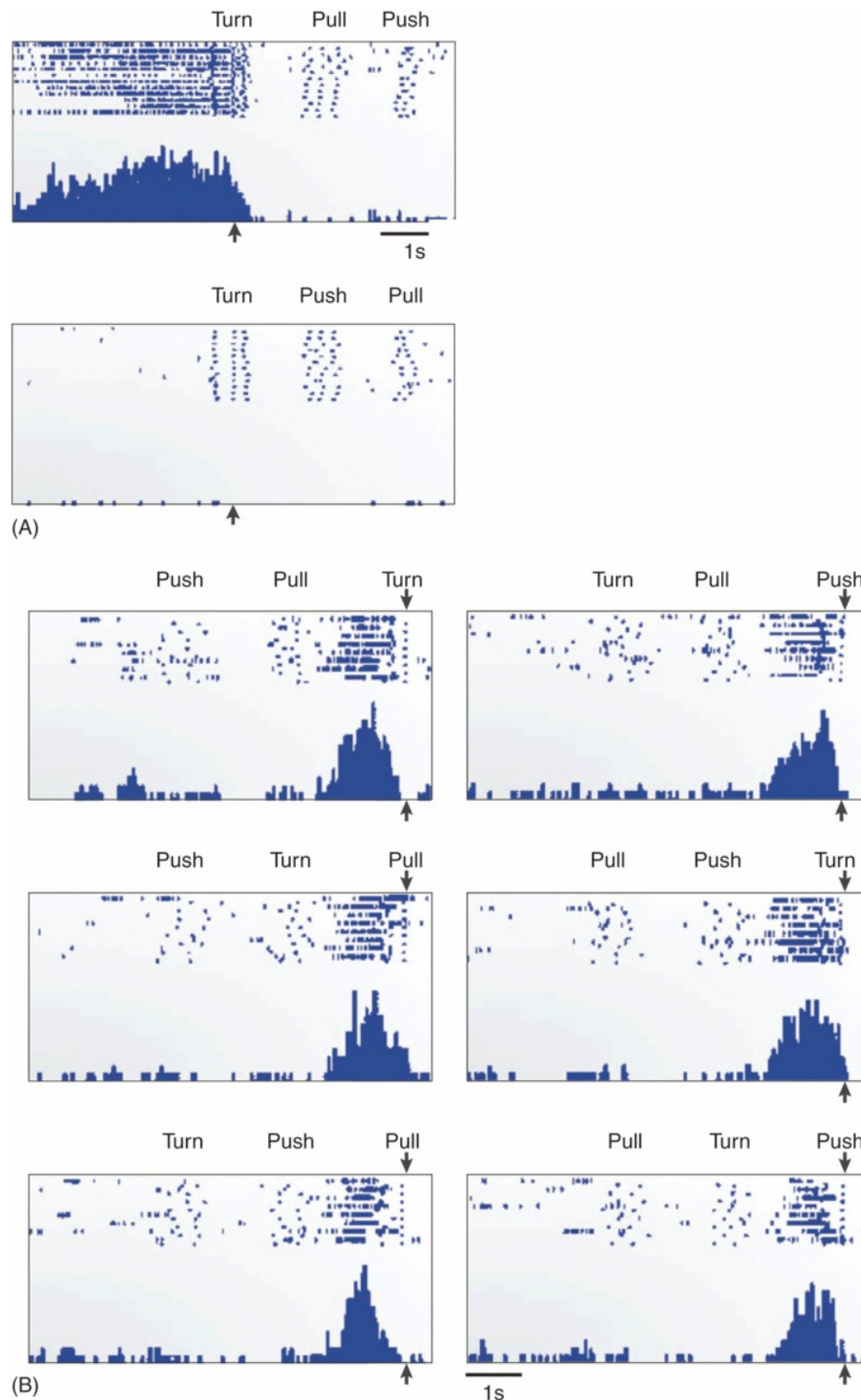


Figure 4.14 Single-cell recordings demonstrate the role of SMA and pre-SMA in motor planning.

(A) Shown here are two recordings from a neuron in the SMA of a monkey. Along the x axis is time and along the y axis is the firing rate. The onset of the action is shown by the arrow. (Top) Notice that when the action sequence requires a turn followed by a pull, the neuron fires intensely prior to initiation of the action. (Bottom) In contrast,

if the turn is followed by a push, no such activity is observed; there is little or no activity prior to onset of the action. This recording demonstrates that SMA is involved in the planning of actions (because the activity precedes the onset of the action) and in planning particular sequences (because the cell's activity depends on the sequence pattern).

(B) Shown here are recordings from a cell in pre-SMA. This cell fires just prior to the initiation of the third action in the motor sequence, regardless of what motor action is third in the sequence (i.e., push, pull, turn) and regardless of what action precedes it (i.e., push, pull, turn). These findings provide evidence that pre-SMA codes for action sequences in a more abstract manner than SMA.

Source: Adapted by permission from Macmillan Publishers, LTD: Tanji, J. and Shima, K. Role for supplementary motor area cells in planning several movements ahead. *Nature* 371, 413–416 ([1994](#)).

Research with humans suggests that the SMC is specifically involved in the planning of complex but not simple movements. Some of the earliest studies examining this issue used PET. They found an increase in SMC activity when, for example, an individual had to repetitively touch the thumb of one hand to the fingertips in a 16-sequence set of movements. However, no increase in SMC activity occurs during a simple repetitive task, such as pressing a spring between the thumb and index fingers once per second. This activity is observed even if the person imagines performing a complex series of movements, without any concomitant motor action (Roland et al., [1980](#)) or when, during self-paced movements, individuals are attending to their intention to make the next move, as compared to actually making the movement itself (Lau et al., [2004](#)). If one must alter a plan of action, SMC activity is also observed presumably because new motor programs must be generated.

Unlike motor cortex, whose output is mainly contralateral, each SMC projects to both the ipsilateral and the contralateral motor cortex, as well as to the contralateral SMC. This neuronal wiring allows one SMC to influence motor control on both sides of

the body. Whereas unilateral damage to the primary motor areas produces difficulties only on the contralateral side of the body, unilateral damage to the SMC in nonhuman primates mainly produces difficulty in bimanual coordination. These animals are unable to execute different movements of the fingers on each hand because the hands no longer work independently, but rather tend to make the same movement at the same time. The deficits are abolished when the corpus callosum is sectioned, a finding that suggests that connections between the SMCs in each hemisphere are important for coordinating hand movements (Brinkman, [1984](#)). In humans, activity in the SMC also is linked to the planning of movement of both hands. Even in tasks in which only one hand is moving, an increase in activation occurs bilaterally over the SMC in each hemisphere (Immisch et al., [2001](#)). This pattern contrasts with that observed for primary motor cortex for which activation is predominantly observed contralateral to the hand that is moving.

Premotor Regions

The [premotor area](#) is aptly named, not only because it is located on the lateral surface of the brain just in front of primary motor cortex, but also because its role is to send commands to the primary motor area, making it just prior in the chain of command. During the production of an action, activity in premotor cortex looks qualitatively similar to that in primary motor cortex. However, the premotor cortex, like the SMC, differs from primary motor cortex in that it exhibits activity prior to the onset of the movement, during which time it may code for multiple potential movements.

Research with monkeys suggests that the premotor region can be divided into two somewhat distinct regions with somewhat distinct roles: the dorsal premotor area (PMd) and the ventral premotor area (PMv). Broadly speaking, the PMd processes the motor significance of sensory cues, coding what type of motor action should be chosen or selected based on sensory information. For example, based on visual characteristics, you would plan a different type of grasp to pick up a pencil as compared to a cup. The PMv appears to be involved in implementing these motor programs and adjusting them so that objects can be manipulated. For example, some aspects of a grasp, such as the

slipperiness of an object or how heavy an item is, cannot be determined by visual cues alone and can only be discerned once contact has been made with the object (see Chouinard and Paus, [2006](#), for a longer discussion).

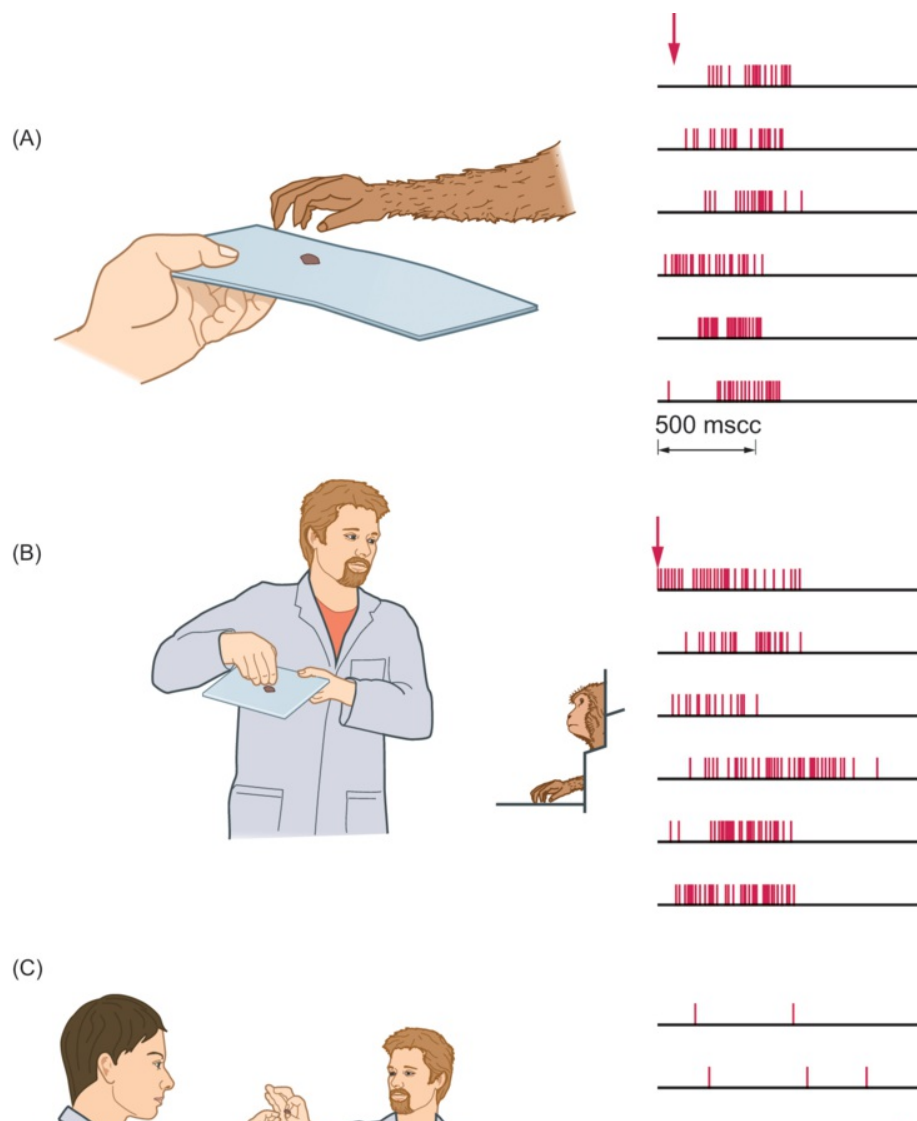
One portion of dorsal premotor regions is known as the [frontal eye field \(FEF\)](#), which, as its name suggests, controls the voluntary execution of eye movements (Vernet et al., [2014](#)). These eye movements include scanning the visual world, such as when you look for a friend's face in a crowd, and visually pursuing a moving object, such as when your gaze follows a bird in flight. As with other premotor areas, the FEFs are involved in planning eye movements. For example, they are particularly involved when one must predict where a constantly moving item is going to go next and planning eye movements to that location (Ilg and Thier, [2008](#)).

The voluntary eye movements controlled by the frontal eye fields are distinct from the reflexive eye movements that occur when a loud noise or a large, bright, moving object pulls a person's attention to a particular point in space. Reflexive eye movements are under the control of the superior colliculus (discussed in [Chapter 10](#)). The neural system controlling voluntary eye movements (involving the frontal eye fields) and the system controlling reflexive eye movements (involving the superior colliculus) can work independently. For example, eye movements that occur when the frontal eye fields are stimulated in the monkey are not affected by removal of the superior colliculus (Schiller et al., [1980](#)). Yet, both of these systems synapse on brainstem centers that direct the actual eye movements by means of the third, fourth, and sixth cranial nerves. Thus, the neural control of both voluntary and involuntary eye movements appears to occur through a final common output pathway, even though they can work separately.

If each of these two systems can control the eye-movement centers in the brainstem, why doesn't massive conflict occur? The conflict seems to be avoided because the frontal eye fields have precedence: they strongly influence the superior colliculus. In humans, damage to the frontal eye fields makes it difficult to suppress automatic eye movements that occur when an attention-grabbing stimulus appears in the periphery,

because the frontal eye fields cannot inhibit the response (Paus et al., [1991](#)). In monkeys, cells in the frontal eye fields excite the cells in the superior colliculus that are important for moving the eyes in the same direction while inhibiting the cells important for movements in other directions (Schlag-Rey et al., [1992](#)). (For a nice review of the different portions of motor cortex involved in eye movements, see Schall and Boucher, [2007](#).)

Research with monkeys has identified a special set of neurons within the PMv known as [mirror neurons](#). These neurons fire both when a monkey performs a particular action but intriguingly also when the monkey observes another organism performing that same action, that is, when the monkey's behavior is mirrored (see [Figure 4.15](#))!



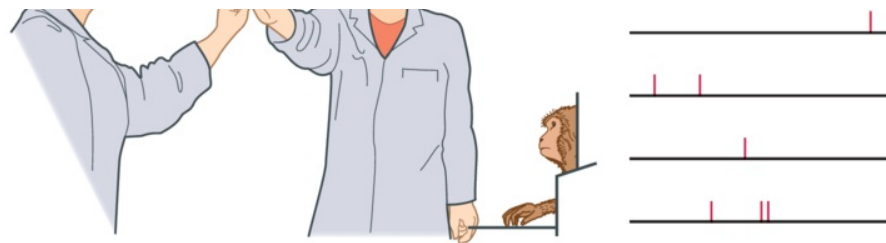


Figure 4.15 The activity pattern of mirror neurons.

Mirror neurons fire not only when the animal engages in a motor action, such as grasping food (top), but also when viewing the experimenter engaging in the same action (middle). However, the cell does not fire when the monkey observes a different motion (bottom). Shown here are six distinct recordings, one per line, for each condition (grasping, watching a grasp). Time is indicated along the x axis and neural activity by vertical lines. The onset of the grasping motion is indicated by the arrow.

(from di Pellegrino et al., [1992](#))

In some cases, the correspondence between the performed and the observed actions must be very tight in order for the mirror neurons to respond to both. For example, a mirror neuron will fire only when the same precision grip involving the index finger and thumb is used both by the monkey and the experimenter. In other cases, the activation is broader: any type of hand grasping by the experimenter will cause neural firing. Activity in these neurons will not occur just by viewing the object, by watching another animal mimicking a gesture, or by observing an action that is directed toward an object (Rizzolatti and Fogassi, [2014](#)). Furthermore, mirror neurons may help to process information not only about the actions of others, but also about ourselves. For example, these cells not only respond when performing an action similar to that made by another, but also exhibit more activity for actions that occur in the light, when the monkey can see its own hand, than in the dark, when a view of its hand is obscured (Bonini, [2016](#)). While mirror neurons are most often associated with PMv, more recent research suggests that cells in other brain regions, such as the parietal lobe, may also exhibit similar characteristics (Kilner and Lemon, [2013](#)).

Neuroimaging studies with humans suggest that the human brain also contains neural regions that are involved in the mirroring of action. Researchers find greater activation in Brodmann area 44 in humans, typically considered Broca's area and the likely human analog to PMv, when hand motions must be imitated as compared to just being observed (e.g., lifting a specific finger in response to seeing that finger being lifted in a video, as compared to lifting a specific finger in response to seeing a photograph of fingers with an "x" on the finger that should be lifted) (Iacoboni et al., [1999](#)). Brain activation is evident as long as the action being observed falls within a person's motor repertoire, regardless of the species producing it. For example, greater activity in Brodmann area 44 is observed when a person sees a video clip of either another person, a monkey, or a dog biting an object, compared to a static image of the biting action. If the motor behavior is not typical for humans, less activity is observed. For example, activity in this region is observed to a greater degree while an individual watched someone reading out loud, to a lesser degree when the individual watched a monkey smacking its lips, and not at all when the individual observed a dog barking (Buccino et al., [2004](#)). Suggesting a critical role for these ventral frontal regions in mirroring the behavior of others, TMS to this area disrupts the ability to imitate finger movements (Heiser et al., [2003](#)). Like more recent studies with monkeys, there is also evidence in humans that regions beyond PMv, once again extending to parietal areas, show activity to the observation of action in others (Molenberghs et al., [2012](#)).

What purpose would such mirror neurons serve? One prominent idea is that they provide a neural substrate for understanding actions being performed by others and for imitating them. It has been argued that this ability is a basic prerequisite for any communication system: one must be able to understand the motor production of another individual in order to imitate it (Rizzolatti and Arbib, [1998](#)). We will return to this idea in [Chapter 8](#) on language. In addition, it has been argued that this system may help an individual understand not only the goal of the motor act, but also the intention behind it. For example, your reaction is likely to be very different if someone appears to grasp a

cup in a manner suggesting he is about to take a sip from it as compared to grasping a cup in a manner that suggests he is about to throw it at you! As such, mirror neurons may also play a role in social cognition (Iacoboni and Dapretto, [2006](#); Rizzolatti and Fabbri-Destro, [2008](#)), an idea we revisit in [Chapter 13](#). Nonetheless, despite how intriguing these ideas are about the potential roles that mirror neurons might play in human cognition, they remain somewhat controversial (see Hickok, [2009](#), [2013](#) for critiques of these ideas). For example, humans with damage to left inferior frontal regions it has been argued that do not show deficits in action understanding, and other neural mechanisms besides mirror neurons aid in action understanding. Hence, it remains for future research to help to clarify the role of the mirror neuron system in action and cognition.

Anterior Cingulate Cortex

The role of the anterior cingulate cortex in cognitive functioning remains one of the most hotly debated topics at present. Until fairly recently, the function of the cingulate in humans was mostly a mystery. Because of its location on the midline of the brain, it was rarely damaged in isolation, making it nearly impossible to determine the effect of a lesion to this region. Since the advent of brain imaging techniques, though, its important role in cognitive function has become much more obvious. Even a cursory look at the brain imaging literature reveals that the cingulate becomes activated across a huge range of tasks. The debate regarding cingulate function probably occurs in part because this structure covers a large expanse of brain tissue. Although referred to in general terms as the anterior cingulate, it has many distinct regions. Some of these regions are more likely to be involved in attentional control and emotional regulation, which we discuss in [Chapters 10](#) and [12](#), respectively. Here we focus on the role that the anterior cingulate plays in motor control.

While premotor and SMC regions are involved in planning movements in general, posterior portions of the anterior cingulate cortex (ACC) aid in the control and planning of movements. This is especially the case when such movements are novel or require

cognitive control, such as when a well-engrained response must be overridden. The posterior portion often co-activates with other key motor regions, such as primary motor cortex (de la Vega et al., [2016](#)). Indicating its linkage to motor function, lesions of the cingulate cortex interfere with motor function. Conversely, extra activity in this region, such as that generated during epileptic seizures, causes increased motor activity while stimulation of the anterior cingulate gyrus in monkeys leads to vocalization as well as to movements of the body, some of which are complex (e.g., sucking) (Vogt et al., [1992](#)).

Evidence from neuroimaging illustrates the more specific role that the anterior cingulate cortex plays in modulating motor commands in humans when the movements to be produced are novel or unrehearsed and therefore influenced by cognitive factors (Paus, [2001](#)). In one of the first such demonstrations, scientists used PET scanning to record regional brain activity while people performed motor tasks that required manual (hand), oral (mouth), or ocular (eye) movements (Paus et al., [1993](#)). For each manner of movement (oral, manual, or ocular), the researchers administered two types of tasks: one that was well practiced and one that was not. For example, in the well-practiced oral task, after hearing “A,” subjects responded “B,” or after hearing “L,” they responded “M.” In the novel task, the stimuli were the same, but the task demands were different. In this task, when individuals heard “A,” they responded “M,” and when they heard “B,” they responded “L.” Cingulate activation was much greater for the novel task than for the well-practiced one.

The study also revealed that the motor portion of the anterior cingulate cortex has a specific topography. Tasks requiring manual movements activated different regions than those requiring ocular movements, which were also distinct from those requiring speech. Thus, like the organization of primary motor and premotor areas, the organization of the anterior cingulate region appears to be topographic.

More recent research has identified three distinct motor zones within the posterior portion of the anterior cingulate, each of which has its own topographic organization

with regards to the effector involved (i.e., subregions for hand, face, eyes) (Amiez and Petrides, [2014](#)) (see [Figure 4.16](#)).

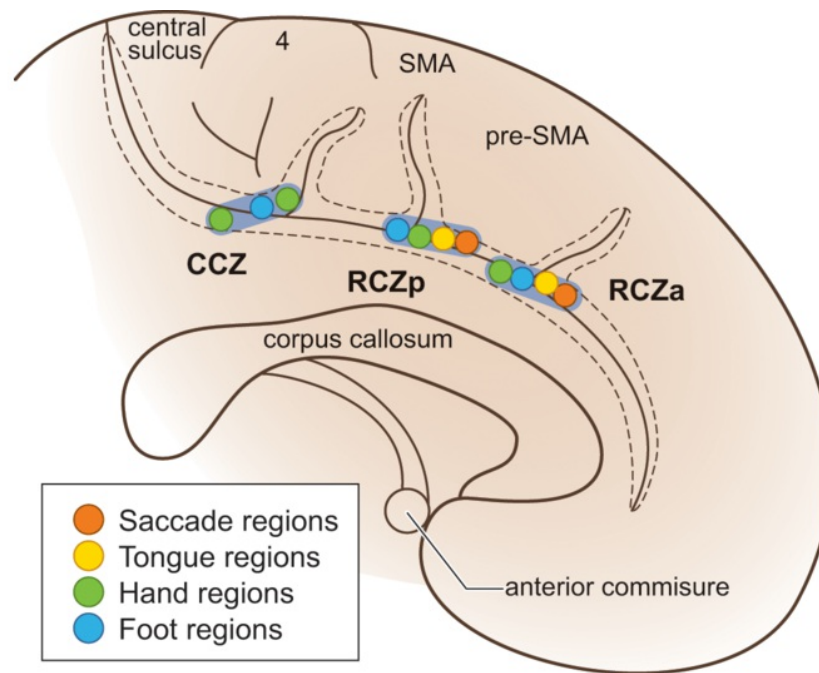


Figure 4.16 Topographic organization of hand, face, and eye regions within each of three distinct zones of posterior sections of the anterior cingulate cortex.

As shown here, there is a topographic organization such that activity related to the hand, face, and eyes are associated with distinct portions of each of three regions within the posterior part of the anterior cingulate cortex.

(from Amiez and Petrides, [2014](#))

But why have three separate motor regions in the anterior cingulate, each with the same redundant topography with regards to effectors? These regions may play somewhat different but complementary roles in motor control (Picard and Strick, [1996](#)) due to the nature of their anatomical connections (Beckmann et al., [2009](#)). The most caudal region connects mainly to primary motor cortex and the parietal lobe and may modulate or override activity during simple motor tasks. The middle region connects primarily to premotor cortex and may modulate the selection of movements. Finally, the most anterior region connects primarily to dorsolateral prefrontal cortex and may

modulate more complex motor actions or become active when a high degree of conflict exists.

Some of our own work (Milham et al., [2001](#)) has nicely illustrated this last point. In our study, individuals had to press one of three buttons to indicate the ink color (blue, green, yellow) in which a word is presented (e.g., “green” in blue ink), a task called the Stroop task, which is known to activate the anterior cingulate. We compared regional brain activation for three types of trials: incongruent trials in which the distracting word names a competing response (e.g., the word “blue” appears in yellow ink, when response options are blue, green and yellow); incongruent trials in which the distracting word names a different color, but not a competing response (e.g., the word “red” in blue ink); and neutral trials in which the distracting word had no relationship to color (e.g., the word “lot” in blue ink). We reasoned that if the anterior cingulate is specifically involved in response-related processes, it should show more activation when the color word names a competing response than when it does not. Furthermore, as long as the word does not conflict with the response, activation should be similar whether or not the word names a different color (e.g., whether the word is “red” or “lot”). Indeed, we found that posterior portions of the anterior cingulate exhibited exactly such a pattern of activity, reinforcing the idea that it plays a prominent role in response-related processes.

The motor system must be able not only to generate and select a response, but also to evaluate the consequences of that choice. The anterior cingulate appears to play a central role in this process. Currently there is a fair amount of debate about exactly how the anterior cingulate evaluates actions. Some theories suggest that the cingulate is involved in detecting conflict including conflict between potential actions (e.g., Botvinick et al., [2004](#)). Other theories posit that it is involved in determining whether an error has been committed (Taylor et al., [2007](#)). Still others argue that the anterior cingulate evaluates whether the outcome of an action produced the expected consequences, that is, was in line with expectations (Alexander and Brown, [2011](#)).

Currently it is not clear whether or not the regions of the cingulate that are involved in overriding or selecting atypical responses are the same as those that aid in evaluating performance (Stevens et al., [2009](#) and Procyk et al., [2016](#) for a different viewpoint). We discuss the role of the anterior cingulate in evaluating performance in more detail in [Chapter 11](#) on executive control.

Right Inferior Frontal Cortex

Not only is it important to be able to sequence and direct motor actions, but on occasion it is also necessary to interrupt or stop an ongoing motor action. One prominent theory suggests that the right inferior frontal lobe, more specifically BA 44 and 45 (also referred to as ventrolateral prefrontal cortex [VLPFC]), has a special role in such control over motor action (for review, see Aron et al., [2014](#)).

A variety of converging evidence supports the role of the right inferior frontal cortex in interrupting or inhibiting motor actions. The ability to inhibit actions is often assessed via a task known as the stop-signal paradigm, in which participants are told to press a button whenever a stimulus appears. However, on a minority of trials, a tone (or some other cue) occurs after the stimulus, and signals that individuals should now interrupt or abort their motor action. This cue serves as the “stop” signal. Numerous neuroimaging studies have reported activity in right inferior frontal regions for conditions in which actions must be interrupted (i.e., the stop-signal trials). Such effects are found regardless of what type of movement must be disrupted, either manual or ocular (e.g., Leung and Cai, [2007](#)). Moreover, rTMS over right inferior frontal cortex interferes with the ability to inhibit a response (Chambers et al., [2007](#)) and recording directly from the brains of individuals (who are typically undergoing surgery for epilepsy) called electrocorticography reveals activation in the right inferior frontal gyrus prior to the completion of the stopping process (Swann et al., [2012](#)). These findings are consistent with effects observed in patients who have sustained brain damage to the right inferior frontal region. The larger the amount of damage in this region, the more difficulty the patients have in stopping their behavior (Aron et al., [2003](#)) (see [Figure 4.17](#)).

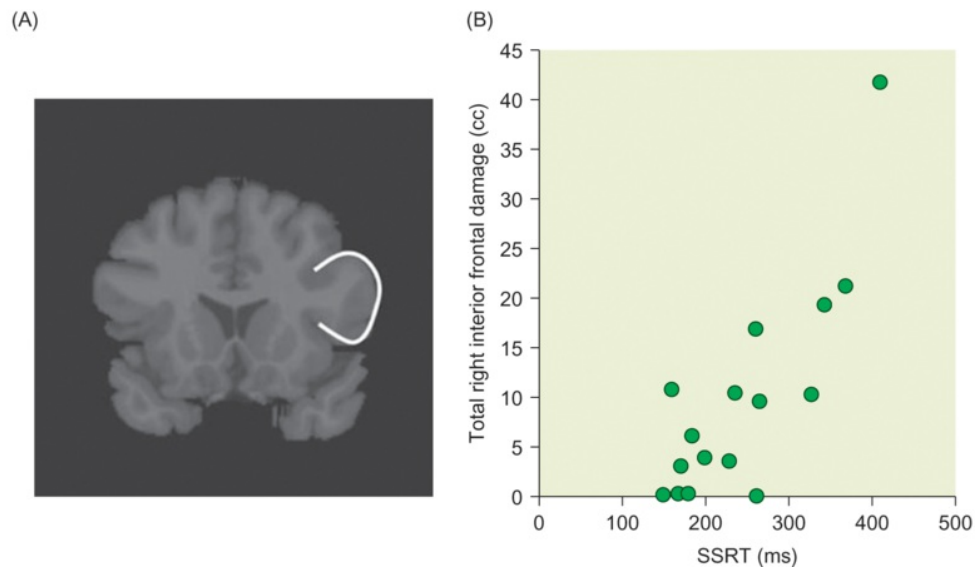


Figure 4.17 The role of right inferior frontal cortex in the inhibition of response.

(A) The region of right inferior frontal cortex that has been implicated. (B) The larger the volume of tissue loss in right inferior frontal cortex (shown on the y axis), the greater the difficulty in inhibiting responses, as indexed by the stop-signal reaction time (SSRT) on the x axis. The SSRT provides an index of how quickly an individual can abort a motor response after a signal to do so has been provided.

Yet some scientists have argued that the role of the right inferior cortex is not specific to response inhibition. For example, most experimental paradigms that involve response inhibition require individuals to inhibit responses on a minority of trials. Therefore, right inferior frontal cortex could be implicated in these tasks not because it is involved in inhibition per se, but rather because it processes information signaling low-frequency events (see, e.g., Chikazoe et al., [2009](#)). Others have argued that the right inferior frontal lobe plays a role not necessarily in inhibiting actions, but rather in selecting them based on the current environmental context (Chatham et al., [2012](#)). For example, the right inferior frontal cortex becomes active not only when a cue signals that an action, such as a single button press, should be inhibited or aborted, but also when a cue indicates that an action needs to be altered in some other manner, such as indicating that a double rather than a single button press is required (Chatham et al.,

[2012](#); Hampshire, [2015](#)). At present, the debate around this issue continues, and we revisit it in [Chapter 11](#).

Parietal Lobe

The role of the parietal lobe in motor programming is twofold: First, it is involved as an interface between movement and sensory information; second, it contributes to the ability to produce complex, well-learned motor acts. These two aspects of motor control appear to rely on different regions of the parietal lobe, the former on the superior regions and the latter on the inferior regions. These regions, and the intraparietal sulcus that divides them, are depicted in [Figure 4.18](#). As demonstrated in both monkeys and humans, the superior parietal lobe acts to integrate sensory information with movements so that the limbs or eyes can be guided correctly during motor acts. To do so, information from spatial maps in different modalities must be integrated. (We discuss much more about the role of parietal regions in spatial cognition in [Chapter 7](#).) For example, when a person reaches for an object, the object's location is taken from visual information and is in eye-centered coordinates. It must be translated into a spatial map in hand-centered coordinates so that the motor action can be directed to the correct location.

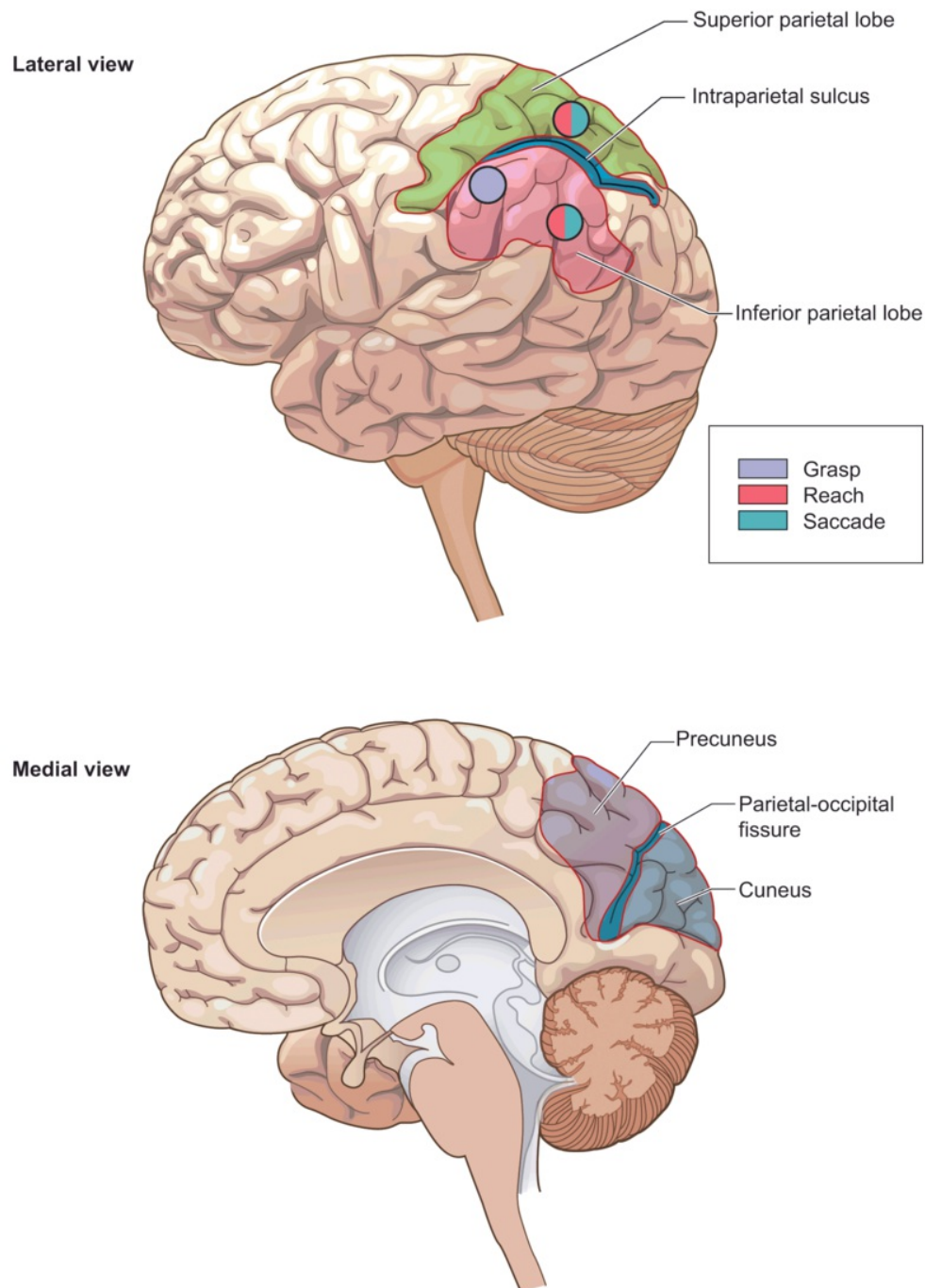


Figure 4.18 Superior and inferior regions of the parietal lobe involved in motor programming.

(A) In both monkeys and humans, the superior parietal lobe (SPL) is important in controlling movements in space, whereas the inferior parietal lobe (IPL) is important in the ability to produce complex, well-learned motor acts. Neuroanatomically, they are divided by the intraparietal sulcus (IPS). Grasping of objects tends to rely more on anterior regions of the IPL, while reaching or moving the eyes tends to rely on

overlapping areas of the SPL. (B) Reaching that is guided by proprioceptive cues tends to rely on more anterior regions of the precuneus whereas those guided by vision rely on regions closer to visual cortex, such as the cuneus.

(adapted from Vesia and Crawford, [2012](#))

It appears from single-cell recordings that there is a sensitivity gradient across cells in the superior parietal lobe with regard to these two frames of reference (those that are eye-centered and those that are hand-centered). Cells that are most sensitive to the difference between the target and hand position are located more toward the dorsal surface of the brain, whereas those located more ventrally appear to be coding the position of items in an eye-centered coordinate system. Some researchers suggest that this organization allows direct mapping from eye-based to hand-based coordinates (Buneo et al., [2002](#)); others argue that there must be an intermediate transformation into head- or body-based coordinates (e.g., McIntyre et al., [1997](#)). Regardless, it is clear that the parietal region is involved in transformations that allow information in a coordinate system based on the sensory world to be imported and transformed into a coordinate system that is body-based and allows control of motor action (for a review, see Buneo and Andersen, [2006](#)).

Parietal regions are sensitive to both proprioceptive information, a type of sensory information received from internal sensors in the body, such as that about the position of body parts relative to one another, and kinesthetic information about actual movement of body parts. Proprioceptive information can be sent forward to premotor and primary motor regions to enable the selection of appropriate motor programs, which in turn provide feedback to parietal regions. The motor feedback, as well as proprioceptive and kinesthetic information, can be used to ensure that movements are being executed according to plan and to enable correction if they are not. (The classic work in this area was performed by Mountcastle and colleagues, [1975](#).)

Damage to the superior parietal region in humans causes individuals to lose the ability to guide their limbs in a well-controlled manner, and is often accompanied by a

tendency to misreach (Levine et al., [1978](#)). In concordance with animal studies, functional imaging studies also provide evidence that different regions of the parietal lobe are sensitive to the type of cue that aids in reaching. More anterior and medial regions of the superior parietal lobe (often referred to as the precuneus) appear to use proprioceptive information to guide reaching, whereas a more posterior parietal region bordering on the occipital region relies more on visual information (refer to [Figure 4.18B](#)). This difference in activation across regions has been shown both in individual studies that directly contrast the two conditions (Filimon et al., [2009](#)) and in a meta-analysis of functional imaging studies (Blangero et al., [2009](#)). Along with findings from studies with brain-damaged patients who have difficulty in reaching, these imaging studies implicate the superior parietal lobe in guiding reaching behavior. These same areas of the brain are also involved when one must direct the eyes to a position in space, via a [saccade](#), much as one moves the arm to a position in space (Vesia and Crawford, [2012](#)).

But what good is being able to reach toward an object, such as a cup of coffee, if you cannot then actually manipulate that object to, for example, turn the cup, grab its handle, and get that steaming cup of coffee to your lips? The brain appears to have a somewhat distinct neural substrate for grasping, which relies on regions in the anterior intraparietal sulcus, located just ventrally, to the superior parietal lobe (refer back to [Figure 4.18](#)). TMS applied to this region impairs the ability to grasp objects (Rice et al., [2006](#)), and activation in this region occurs to a greater degree for grasping than reaching movements (Frey et al., [2015](#)). This region appears to code for the abstract representation of a grasp as these effects are observed regardless of the effectors (i.e., muscles) or the movements required to form the grasp.

Damage to more inferior regions of the parietal lobe can affect the ability to perform complex, well-learned motor acts, a disorder known as apraxia. Apraxia is a syndrome in which an individual is unable to perform certain complex, learned motor tasks when asked to do so (Lezak et al., [2012](#)) despite intact motor innervation of the muscles, an intact ability to coordinate sensorimotor actions spontaneously, and an ability to

comprehend what is being asked. The neural control of complex movement is lateralized, because apraxia often results after damage to the left inferior parietal lobe. Apraxia is discussed in more detail later in this chapter.

Researchers have hypothesized that the left parietal lobe links different types of information, such as visuokinesthetic information and internal conceptual representations, to motor plans. Considered this way, the performance of complex, learned acts falls well within the domain we characterized in [Chapter 1](#) as the purview of the parietal lobe – namely, that of a multi-modal association area. For example, the inferior parietal lobe might link the visual and kinesthetic information of a match and a matchbook cover with the motor act that involves lighting the match using the matchbook cover. Such linkages do not require a physical object, because the parietal lobe may also link motor acts to internal representations such as those occurring during pantomime or gesture (e.g., waving goodbye) (Heilman and Rothi, [1985](#)).

Given the deficits in pantomime and gesture after parietal damage, this region may be critical for generating a mental model of movements. For example, patients with parietal lobe lesions were asked to imagine pressing each finger against the thumb sequentially in beat with a metronome whose speed was increased every 5 seconds. The participants were asked to determine the speed at which, in their imagination, their fingers moved quickly enough keep up with the metronome. Their estimates were quite poor compared to their actual performance on the task, indicating that their mental model of movements had been disrupted (Sirigu et al., [1996](#)). Likewise, neuroimaging studies indicate that the left inferior parietal area (BA 40) becomes active when an individual has to imagine making complete sequential movements of the finger (Gerardin et al., [2000](#)). This same region is involved when one must plan and imitate the use of a tool, regardless of whether performed by the right hand or the left (Johnson-Frey et al., [2005](#)). The fact that the left hemisphere is activated regardless of the hand employed suggests that a motor control system for mental models of movement is mainly lateralized to the left hemisphere, consistent with the location of the lesion that causes apraxic behavior.

How are these mental models different than the mental models of movement that we discussed earlier with regards to the cerebellum? You may remember that the cerebellum is involved in creating a forward model that helps to predict the sensory consequences of motor plans (e.g., I am experiencing what I anticipated). For example, if you decide to pick up a full carton of milk from a table, you have a model of how it should feel when you do so and how much force you will need to pick it up. But what happens if the carton turns out to be empty? As we discussed earlier, the cerebellum does not seem to be able to make such adjustments after an action is initiated.

Rather, the left parietal lobe appears to play a large role in this adjustment process (Desmurget and Grafton, [2000](#)). This role of the parietal lobe in movement adjustment was demonstrated in a study in which people were to move their arms to a visual target. Unbeknownst to them, after they started to move their arms, the target's location was moved. They therefore needed on-line adjustment of the motor program, based on the change in visual input, to correctly reach the target. If during this time period TMS was applied over the left posterior parietal cortex to disrupt activity in this region, no adjustments were observed for the contralateral arm movement – it was incorrectly directed to the same position where the target originally was located (Desmurget et al., [1999](#)).

Researchers have suggested that this adjustment process can occur because the parietal lobe plays a role in state estimation, that is, it estimates and keeps track of where the limbs and targets are in space, and potentially also where they are relative to each other. Rather than predicting the sensory states to be expected based on a motor program (a forward model), in this case you estimate the motor actions that are required to reach a particular state. For example, consider the act of serving a tennis ball on a windy day. As we discussed earlier, our cerebellum creates a forward model of the anticipated sensory feedback from a motor action, such as how it will feel when the racquet meets the ball. The parietal lobe, in contrast, provides an estimate of how the limbs must be moved so that they reach the target position, in this case, so the racquet meets the ball. This estimate does not dictate an exact trajectory for limb movement, but

allows for flexible execution in the face of perturbation. Consider, for example, that after you toss the ball, a strong gust of wind comes along blowing the ball sideways. You now need to compute the new location of the ball, guided by sight, and integrate that information with an estimate of what movements will be now be required to hit the tennis ball at its new location. This is where your parietal lobe saves the day! (See Wolpert et al., [2011](#), for a discussion of the range of computational problems that must be solved by the motor system, and the different possible ways of doing so.)

As we have just considered how motor control by the parietal lobe differs from that of the cerebellum, you may now be wondering how the control of movement of the parietal lobe differs from that of the SMC. One suggested difference is that the parietal lobe is more involved in the “wanting to move” aspect of motor control that specifies a general goal to be reached before movement planning, while the SMC is more involved in the “urge to move,” that is, controlling the time when the planned movement is about to start (Desmurget and Sirigu, [2012](#)). In the [next section](#), we briefly review the contribution of different brain regions to motor control and planning and consider how their action may be integrated and coordinated.

Integrated Models of the Motor System

At this point, we have reviewed the major regions of the brain that are involved in movement and have briefly outlined some of the motor disorders that occur after damage to these brain regions. It is important to keep in mind that despite the different roles each brain region plays, there is substantial overlap. For example, sequential movement requires the integrated functioning of many different brain regions. To gain an appreciation for how each of these individual brain regions might contribute to sequential motor processing, see [Table 4.1](#).

Table 4.1 Functions of Major Brain Regions Involved in Movement

| Brain Region | Computation |
|--------------|-------------|
|--------------|-------------|

Movement Planning

| | |
|--|--|
| Inferior parietal regions | Generating an estimate the state of limbs and effectors required for a movement |
| Supplementary motor complex | Selecting and initiating the order of movements |
| Premotor area | Selecting the types of movements required (e.g., a grasp) |
| Frontal eye fields | Voluntarily controlling saccades |
| Posterior regions of the anterior cingulate cortex | Selecting among competing responses, initiating novel responses, and overriding well practiced responses |

Movement Specification and Initiation

| | |
|---------------|---|
| Cerebellum | Creating a forward model |
| Basal ganglia | Switching between different patterns of movement initiation and cessation; chunking motor patterns; modulating movement parameters, such as their vigor |
| Motor cortex | Executing the force and/or direction of movement; driving muscle activity |

Movement Monitoring

| | |
|---------------------------|---|
| Anterior cingulate cortex | Evaluating the outcome of a response (e.g., detecting when an action is erroneous or its consequences are unexpected) |
| Parietal cortex | Using sensory feedback to adjust |

movement on-line

We can consider the contributions of each region from a number of different perspectives. First, we can view them as aiding in different types of movement. For example, we have discussed the cerebellum's importance for movements that are not modified in response to sensory feedback, such as rapid ballistic movements, whereas the basal ganglia and parietal region play roles in modifying ongoing movement. Second, we can consider the roles of these different regions within a hierarchy that contains different representations of movement at different levels of abstraction. For example, we noted that the SMC creates a general motor plan (e.g., pick up the glass of water), that premotor regions specify the type of movement required (e.g., a grasp), and that primary motor regions implement the muscle movements to carry out the plan.

Yet another perspective is derived from computational models of actions, such as models of [optimal feedback control](#) (Scott, [2012](#)). This viewpoint conceptualizes the motor regions of the brain working together as a circuit to reach a goal, which can be met by a number of different movement options. Regardless of what movements are used, attaining those goals requires certain computations, such as estimating the state of the system, predicting the results of actions, determining rewards and costs of action, and optimizing performance.

Theorists have attempted to link the computational requirements of the optimal feedback control model to different regions of the motor circuit. It has been suggested that parietal cortex estimates the state of the system by comparing the expected sensory feedback with the actual sensory feedback. The cerebellum plays a role in building internal models of the sensory consequences of motor commands and modifying those models through learning. The basal ganglia help estimate the costs of motor commands and the reward to which they will lead. And information from the parietal cortex is fed to premotor regions and primary motor cortex to alter the ongoing motor actions if the current ones are not optimal (see Shadmehr and Krakauer, [2008](#)).

How is all of this exquisite information coordinated to enable that simple act of reaching for your cup of coffee? The parietal regions, which estimate the required “state” of the motor system, that is, how limbs and effectors should be positioned for motor actions, have distinct connections to each of the many lateral and medial regions of the frontal cortex involved in motor control. But, as you might imagine, if that information reached those regions simultaneously, chaos might ensue. Recent evidence suggests that there are varying lags in how quickly information can reach each of these areas, influenced by the myelination and diameter of fiber tracts connecting these various regions (see [Figure 4.19](#)). By carefully modulating when information is sent from parietal regions, to specific frontal target sites, that is, with temporally dispersed delays, it is possible to create synchronous activity across regions in service of the motor task (Battaglia-Mayer et al., [2015](#)). Notice that this idea is a bit different than a completely hierarchical and temporally linear model in which the parietal lobe designates exactly where the limbs and effectors should be, the premotor regions code the type of movement to get them there, and then the primary motor regions send a signal to the muscles to execute the command.

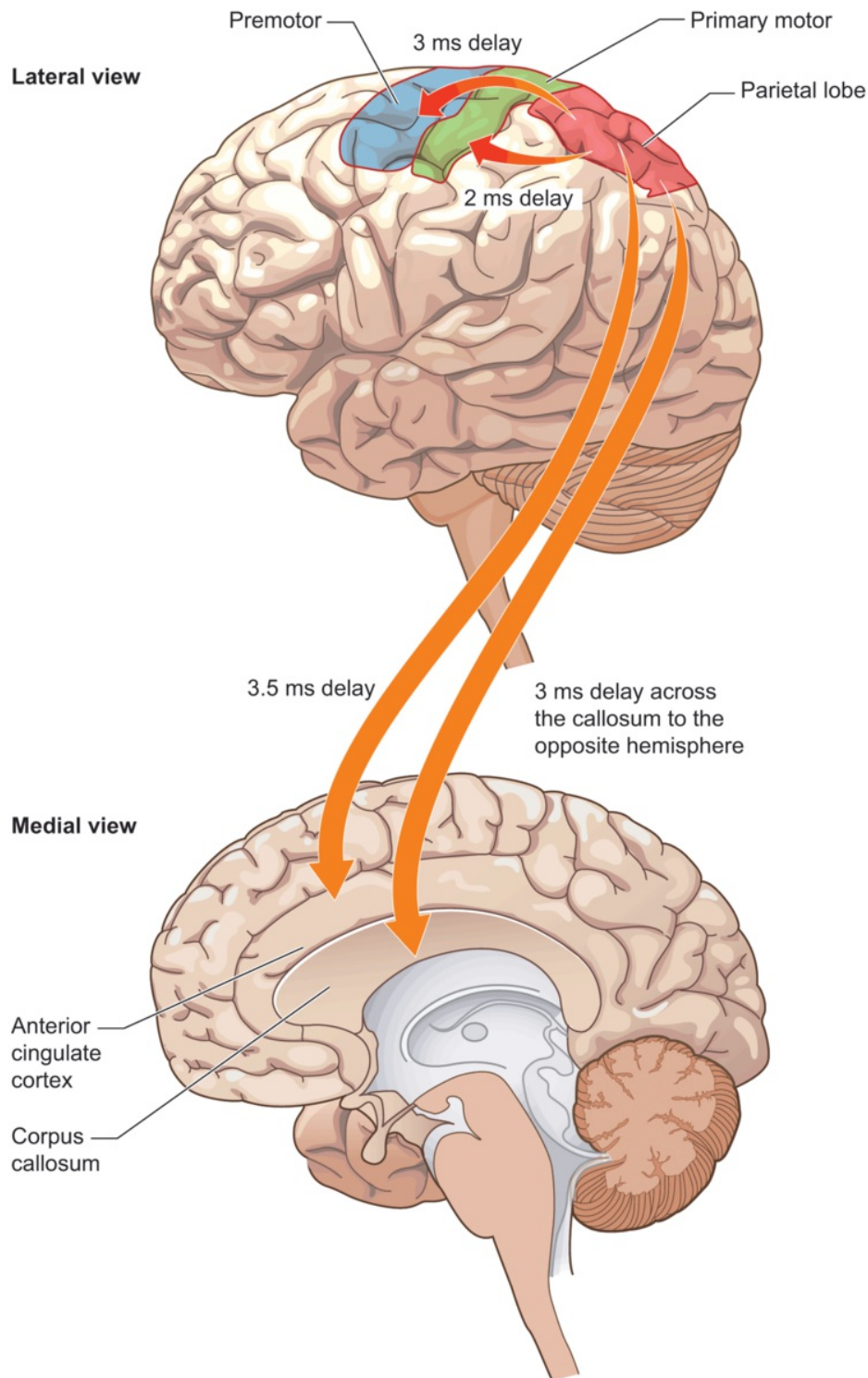


Figure 4.19 Conduction velocity delays between parietal regions and various frontal motor regions.

In planning motor action, the parietal region needs to take into account the delays that are imposed by the connections between it and motor regions in the frontal lobe. These delays are shown here in red, and represent time in milliseconds (ms). Delays

to primary cortex are the order of 2 ms, to premotor regions on the order of 3 ms, and to the anterior cingulate on the order of 3.5 ms. Notice that delays across the corpus callosum, of about 3 ms, are also important to consider as information as motor plans formed by the left parietal lobe are important for movements on both sides of the body.

(from Battaglia-Mayer et al., [2015](#))

You may be asking yourself what are the advantages of such a system compared to the simple hierarchical framework. Such a system allows for flexibility of responding and adaptability depending on changing conditions. For example, in monkeys, two distinct pools of neurons can be activated in premotor regions, essentially coding for more than one possible response. Once relevant information, such as sensory input, that adjudicates between these two potential responses is received, the population activity moves entirely to a state consistent with just one of the response options (Cisek and Kalaska, [2005](#)).

Regardless of which of these models ultimately provides a more compelling account of motor behavior, this discussion underscores a point that we will return to many times in this text: no brain region is an island unto itself. Rather, performance of the complex cognitive abilities demonstrated by the human mind requires many brain regions acting in a coordinated manner.

In Focus: Using Brain Activation to Control Prosthetic Limbs

Imagine a science fiction movie in which the main character is a cyborg – half-human, half-machine. Its hands are shaped to allow it to perform all the actions of a human hand, but they are also outfitted with other features, such as retractable claws for latching, scratching, and climbing, and pinchers that enable grasping and crushing. And how does the cyborg command its bionic arm to make both human and nonhuman motions? By wireless connections that run from

its brain to its arm, so that simply thinking the movement it wishes to produce makes them happen!

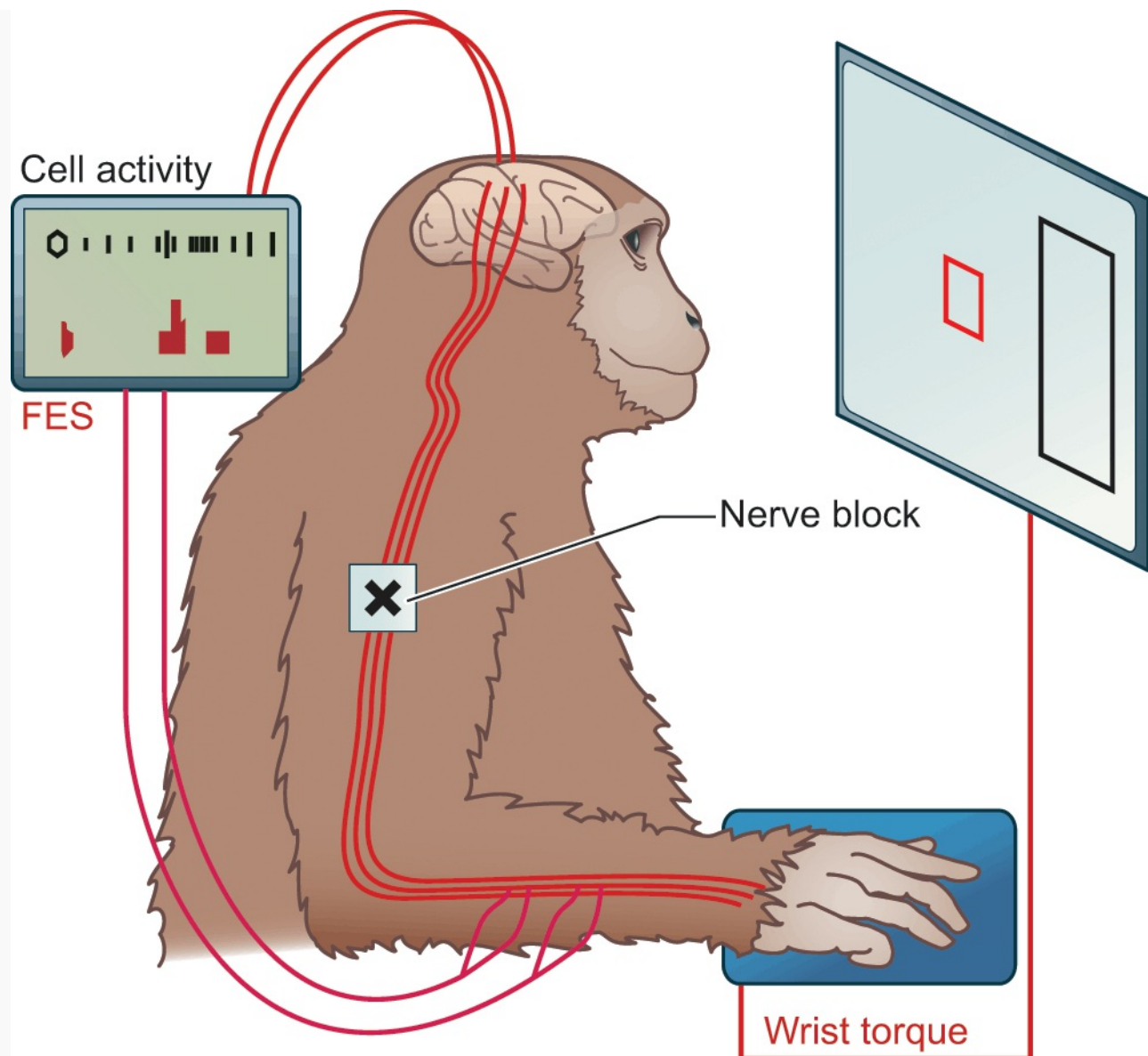
Although this may sound like science fiction, part of this scenario is happening today. Within recent years, there has been a flurry of activity in the creation of brain-computer interfaces, especially those designed to control artificial limbs. To date, most of the work has been confined to rodents and monkeys, but more recent research has demonstrated the utility of this approach in humans as well. These advances have been spurred by greater understanding of the neural mechanisms involved in motor control, increased ability to record brain activity from multiple sites, and the increase in the power and speed of computers, allowing complicated brain activity to be analyzed quickly and processed for output without a delay (often referred to as “real-time processing”). In turn, the quest to build a better brain-computer interface has provided additional insights into the principles of brain structure and function (Nicolelis and Lebedev, [2009](#)).

Some brain-computer interfaces are designed with the idea of using intact motor cortex to send signals either to a limb that has been paralyzed due to spinal cord damage (which precludes the signal from the motor cortex from reaching the limb) or to a prosthetic device (when the limb has been severed) (see Daly and Wolpaw, [2008](#), for discussion of brain-computer interfaces in neurological rehabilitation). As we learned earlier in this chapter, motor control occurs via activity across a population of neurons. Newer multiarray recording technologies allow the pattern of neural firing across such a population to be recorded. In monkeys, such arrays can be placed in primary motor cortex, which controls the movement of limbs, or in premotor areas involved in the planning of motor acts.

The information from neural activity from these different areas is then linked with information on where the animal is reaching. To do this, researchers employ

complex computational algorithms that, over time, learn the association between the neural pattern of activity and the action that is being performed. As a result of such training, the neural signals can then be used to guide movement of a robotic arm (Wessberg et al., [2000](#)). Further research recording from the parietal “reach” area has demonstrated that neural signals can be used to predict the intended endpoint of a reach (Musallam et al., [2004](#)) as well as the trajectory of that reach (Mulliken et al., [2008](#)).

Even more exciting are findings that take electrical output from the brain and use it to control a paralyzed arm (Moritz et al., [2008](#)). In this experiment, electrodes were implanted into the motor cortex of monkeys, and another set was implanted in the wrist so that brain activity could reach the muscles. Monkeys were trained to control the discharge rate of neurons in the brain that control wrist movements, by means of the location of a visual cursor on the screen. In this training, they were rewarded when their performance matched the target rate of discharge. Next, a nerve block was given that disrupted the neural connection between the brain and the wrist. Although the cells in motor cortex continued to fire, no wrist movement was observed, confirming that disruption of the connection between the brain and wrist leads to paralysis of the hand. Then, information from the electrodes in motor cortex was connected directly to the electrodes in the hand, bypassing the blocked neural pathway between the brain and the hand. With some training, the monkeys learned to use the firing rates of cells in their motor cortex to control their wrist movement! (See [Box Figure 4.1](#).)



Box Figure 4.1 An experiment demonstrating brain-controlled functional stimulation of muscle.

In this brain-computer interface, electrodes from motor regions of monkey cortex feed into a computer that analyzes brain activity. The monkey is trained to alter the pattern of brain activity by being rewarded for keeping a cursor in a particular location on the screen. A nerve block then disconnects the signals from the brain from reaching the hand, which is indicated by paralysis of the wrist. Next, the information from the computer is linked to muscles of the hand. After a little practice, the monkey is able to control the wrist just by altering the pattern of brain activity.

Recently this same technique – using intracortical recordings from motor cortex to control muscles of the arm and hand – has been successfully performed in humans. Such a brain-computer interface has allowed a 24-year-old man, who is quadrapelgic as a result of a diving accident, to manipulate, grasp, and release objects (Bouton et al., [2016](#)).

Despite these amazing advances, a number of issues must be overcome before such techniques can be used routinely in humans. For example, if stroke leads to paralysis of the contralateral hand, only one hemisphere remains to control movement of both the contralateral and ipsilateral hands. Therefore, the neural signals that are related to motor activity of the contralateral hand must be distinguished from those associated with the ipsilateral hand. Recent research on patients with electrodes implanted over frontal cortex (for surgery associated with epilepsy) suggests, fortunately, that the neural signatures for ipsilateral and contralateral movements differ. Moreover, it has been demonstrated that individuals can learn to use the pattern of activity associated with contralateral movements to control a cursor, and separately they can learn to do likewise with neural activity associated with ipsilateral movements. These findings pave the way for stroke patients to potentially control a prosthesis or their own paralyzed limb (Wisneski et al., [2008](#)).

But for these methods to be practical for a large number of people (other than those with intracranial electrodes), less invasive methods, such as scalp-recorded EEG, will need to be employed. In one step toward this goal, researchers have used brain signals from scalp-recorded EEG to control not a limb but an external device such as a robot. In the future such an approach might be utilized to use patterns of brain activity to control other devices, such as a patient's own wheelchair (Cincotti et al., [2008](#)). In another advance, scientists have demonstrated that EEG information recorded from the healthy cortex can be used to control the upper limb in patients after stroke (Antelis et al., [2016](#)).

In the end, success or failure of these approaches will probably depend on three factors. First is the issue of whether the brain-computer interfaces can extract enough information from the brain to enable the sophisticated control required for tasks of everyday living without undue risk to the person. Implanted electrodes may provide better fidelity on the patterns of brain activity required for control of a prosthesis, but at the cost of invasive brain surgery. In contrast, the less invasive scalp-recorded EEG may not provide as clean or discrete a pattern of neural signals. These trade-offs will have to continue to be explored. Second, these systems will have to be durable enough to remain intact during the movements of everyday life (outside the closely controlled environment of the laboratory or hospital), and small enough to allow people to move around the world with the interface. Third, it remains to be seen whether such systems will enable movements that occur with the speed, accuracy, and flexibility of an intact system (Ryu and Shenoy, [2009](#)).

Factors about the brain itself, rather than the design of the artificial systems, will also need to be considered. First is the plasticity of the brain and the limits of that plasticity. The brain has a set of intrinsic patterns of activation, for example, when engaging in motor acts. Work with monkeys has shown that such intrinsic patterns can more successfully drive brain-computer interfaces than when new patterns of activation must be learned (Sadtlir et al., [2014](#)). As such, the repertoire of existing activation patterns may limit new learning.

Second, other emerging research indicates that aspects of a person's brain anatomy may also influence how successfully that person can use a brain-computer interface. Individuals with a higher degree of myelination of certain deep white-matter tracts like the corpus callosum and cingulum bundle have better success rates in using such devices (Halder et al., [2013](#)). Finally, on the most basic level, better understanding of the exact movement parameters

coded by the motor cortex will likely be required before brain-computer interfaces can work with higher fidelity (Baranauskas, [2014](#)).

Nonetheless, the hope for many people who have lost control of their limbs due to neurological damage, and for those who have lost limbs, is that scientists will make significant headway in dealing with these issues and overcoming these problems in the near future. (For a recent discussion of the use of these devices for individuals with paralysis, and those with stroke, see Chaudhary et al., [2015](#), and Soekadar et al., [2015](#), respectively.)

Motor Disorders

We now turn our attention to the neurological basis of some of the more common motor disorders. In this discussion, we divide motor disorders into two categories: those that occur because of damage or disruption to subcortical areas, and those that occur after cortical damage. As discussed at the outset of this chapter, we can broadly characterize subcortical motor disorders as affecting the form and timing of movements, whereas cortical motor disorders affect the conceptual clarity of motor acts, either by disrupting the sequencing of complex motor acts or by disrupting the ability to have a motor act represent a concept.

Subcortical Motor Disorders

In this section we discuss motor disorders that are characterized mainly by damage to subcortical regions: Parkinson's disease, Huntington's disease, and Tourette's syndrome.

Parkinson's Disease

As we learned earlier, [Parkinson's disease](#) results from damage to the cells of the substantia nigra, which stops producing the neurotransmitter dopamine (for a good

review of all aspects of the disorder, see Kalia and Lang, [2015](#)). After Alzheimer's disease, it is the most common neurodegenerative disorder. The etiology (i.e., the cause) of Parkinson's disease is not certain, although there is general agreement that it results from a complex interaction of genetic and environmental factors. Suggesting a genetic contribution, the disease runs in families, and at least some genetic mutations associated with such familial cases have been identified. Environmental factors associated with the disease include toxins (e.g., pesticides), trauma, and inflammation. Still other cases may be viral in origin. For example, in the 1910s and 1920s, individuals with encephalitis lethargica (also known as von Economo's disease) caught the flu and exhibited Parkinsonian symptoms either soon thereafter or as long as 20 years later.

Parkinson's disease can also be caused by drugs that people voluntarily ingest. For example, in the mid-1980s, young adults in their twenties and thirties began appearing in hospital rooms exhibiting symptoms of the disease, especially those related to lack of movement. Because such symptoms are highly unusual in this age group, doctors looked for a commonality among the patients and discovered that all were drug users. These afflicted individuals were dubbed "the frozen addicts." Some detective work revealed that these cases of Parkinson's disease could be linked to a synthetic heroin that was contaminated with the compound MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which, when converted by the body into MPP⁺ (methylphenylpyridinium), is toxic to dopaminergic cells.

The behavioral effects of the disease typically are not evident until 60% of nerve cells and 80% of dopamine are lost (for a review of the pathophysiology of Parkinson's disease, see Bartels and Leenders, [2009](#)). The delay in symptom onset occurs because the brain tries valiantly to compensate for the loss of dopamine in a number of ways, such as by having the remaining dopaminergic neurons increase their synthesis of dopamine or by decreasing the inactivation or clearance of dopamine once it crosses the synaptic cleft (Zigmond et al., [1990](#)). At some point, however, often later in life, when a person reaches age 60 or 70, these compensatory mechanisms fail. At this point, cell

loss, which is a normal part of the aging process, reduces the population of cells in the substantia nigra below a critical point, and behavioral effects are observed.

The movement disorder of Parkinson's disease has four major symptoms: [tremors](#), [cogwheel rigidity](#), [akinesia/bradykinesia](#), and [disturbances of posture](#). These symptoms are generally observed on both sides of the body. However, in some cases, the dopamine depletion occurs in just one half of the brain, so symptoms are evident only on the contralateral side of the body, a condition known as hemi-Parkinsonism.

Tremors are repetitive, rhythmic motions that result from oscillatory movement of agonist and antagonist muscles. They are so predominant that James Parkinson originally called the disease "shaking palsy." Parkinsonian tremors generally affect the arms and hands. These tremors are usually not seen during deliberate and purposeful movements, but are quite obvious when the person is at rest (e.g., just sitting in a chair listening to a conversation). Hand tremors are often described as "pill-rolling" because they resemble movements of an individual who is rolling a pill between the thumb and forefinger.

The rigidity observed in Parkinson's disease occurs because increased muscle tone in the extensor and flexor muscles makes the person appear stiff. In fact, the mechanical nature of the movements is referred to as cogwheel rigidity. If you try to move a limb of someone with Parkinson's disease, the movement is resisted. If you push hard enough, however, the limb can be moved, but only so far until once again the movement is resisted. When sufficient force is applied, the limb can be moved again. Thus, rather than moving smoothly, the limb moves in specific, rigid steps, much as a cogwheel does.

Another symptom of Parkinson's disease is akinesia, a poverty or lack of movement, or bradykinesia, slowness of movement. Some Parkinson's patients sit motionless, like mannequins in a store window. As we saw in the case of Muhammad Ali, this lack of movement can be so severe as to disrupt communication. Speech is affected because individuals have trouble producing sounds, and writing is affected because the production of letters is slow and labored.

Facial movements can also diminish such that individuals are said to have a [Parkinsonian mask](#). One of this text's authors had an experience that illustrates this phenomenon. She and some colleagues were making a presentation to a very well-renowned elderly senior scientist in the field. After the presentation, her colleagues commented that the presentation must have flopped because the senior scientist had not reacted at all, and had sat through the entire presentation with a deadpan expression on his face. She, however, had been sitting close enough to see his hands, which were placed in his lap, and noticed that he was exhibiting the telltale pill-rolling movement. As such, she explained to her colleagues that what they had interpreted as disinterest was probably much more likely but one sign of Parkinson's disease, the Parkinsonian mask.

Parkinsonian symptoms also include difficulty in posture and locomotion. Unlike tremors, which mainly affect the arms and hands, these other difficulties affect muscle groups throughout the body. The posture of a person with Parkinson's disease suffers. Generally, the stance of an individual with Parkinson's becomes more narrow, there is a stooped posture with rounding of the shoulders, the person's head may droop, and there is increased flexion in the knees and hips (Schoneburg et al., [2013](#)). The posture required for sitting or standing may become difficult to maintain without support. [Figure 4.20](#) illustrates an example of how someone with Parkinson's disease appears.



Figure 4.20 The presentation of a person with Parkinson's disease.
Notice the frozen face and stooped, flexed posture.

The ability to make postural adjustments may also be impaired. For example, individuals with Parkinson's disease may fall when bumped because they cannot right themselves quickly after losing balance. Movements that require transitions are also difficult, such as standing up from a seated position or writing in a cursive manner (see [Figure 4.21](#)).

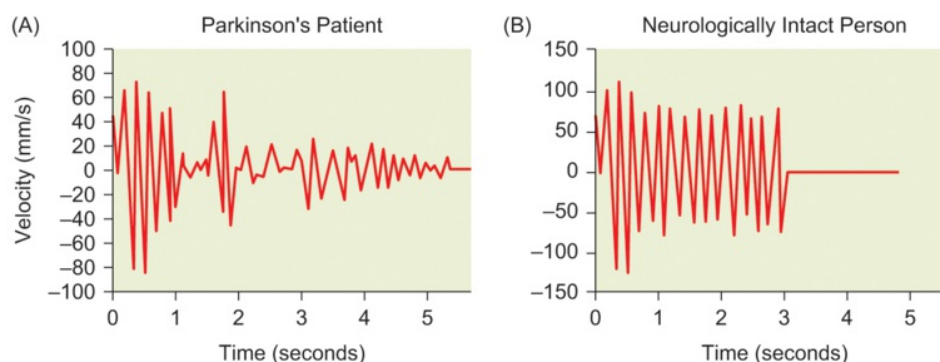


Figure 4.21 The disruption in writing as a result of Parkinson's disease.

The writing of the word "minimum" (A) by an individual with Parkinson's disease, compared to (B), a neurologically intact person. In a person with Parkinson's, the ability to maintain the velocity of the movement as transitions occur across letters is disrupted, whereas in a neurologically intact person the velocity can be kept constant across those transitions.

Walking is compromised not only because it requires continual postural adjustments, but also because it requires a series of movements, which akinesia renders difficult. When patients with Parkinson's disease walk, they tend to shuffle, much as normal people do when walking on ice or in other situations in which maintaining balance is difficult. A person with Parkinson's disease may take a long time to begin to walk across a floor. However, once started, they may be able to maintain that movement albeit slowly.

The initiation of behavior may be aided by stimuli or signals in the environment. For example, patients with Parkinson's will be much better at initiating walking if there are markers on the floor to guide them. Likewise, a person with Parkinson's disease may be unable to initiate the leg movement required to kick a stationary ball, but if the ball is

rolled toward him or her, the ball will act as a trigger, and the person will respond with a kick. (A nice illustration of this phenomenon can be seen in the movie *Awakenings*, starring Robert De Niro and Robin Williams.)

Although Parkinson's disease has been described as having four major symptoms, not all of these symptoms are always observed in any one person. Some patients have a tremor-predominant form, while other forms lack tremor and are referred a rigid-bradykinetic-predominant form or a postural instability/disordered gaits form. These varieties of Parkinson's may differ not only in their behavior, but also in their biochemical bases, in the degree of intellectual impairment observed, and in the clinical course of the disease (Marras, [2015](#)). However, at least some research suggests that an individual's subtype may not stay stable over the course of the disease, leading some researchers to suggest that the tremor-predominant form may be a precursor or early stage form of the disease (Nutt, [2016](#)).

Let's go back and consider how disruption of the basal ganglia might lead to the symptoms of Parkinson's disease. As discussed earlier in the section on the basal ganglia, the classical conception of Parkinson's disease is that it results from overactivity in the indirect pathway, which leads to the cessation of movement. In fact, the severity of rigidity and bradykinesia can be directly predicted by the degree of dopamine depletion as measured by PET (Antonini et al., [1995](#)).

Other research suggests that the causes of Parkinson's disease may be more than just a reduction of activity in the indirect pathway, and may also involve alterations in neural synchrony. Studies of monkeys that have been treated with the toxin MPTP – the same substance ingested by the “frozen addicts” – reveals an increase in the proportion of neurons in the basal ganglia that fire in bursts (Wichmann and Soares, [2006](#)). This bursting pattern can be decreased through treatment with dopaminergic drugs, and a concomitant decrease in Parkinsonian symptoms is seen as well (Heimer et al., [2006](#)). Likewise, recording from the brains of Parkinson's patients about to undergo surgical intervention shows that the reintroduction of dopaminergic drugs (used to treat

Parkinson's) reduces such synchronous bursting activity. The more such synchronous activity is disrupted, the greater the decrease in akinesia and rigidity (Kuhn et al., [2006](#)). These findings suggest that Parkinson's may not be caused solely by a reduction of activity in certain portions of the basal ganglia, but by a change in the activity across neurons within the basal ganglia.

Yet neither of these models can explain the tremor observed in Parkinson's disease. One possibility is that tremor is an attempt at compensation by regions downstream from the cerebellum to compensate for low levels of movement (Rivlin-Etzion et al., [2006](#)). Another possibility is that tremor is caused by the disruption of circuits between the cerebellum and the thalamus. Supporting this idea, lesions of the ventrolateral thalamus, which receives input from the cerebellum, reduce or suppress tremor (Bergman and Deuschl, [2002](#)). Finally, other evidence suggests that a different neurotransmitter system, serotonin, is associated with tremor, and that the depletion of serotonin (rather than dopamine) may predict the severity of tremor (Carette et al., [2008](#)). (For review of current hypotheses regarding the pathophysiology of Parkinsonian tremor, see Helmich et al., [2013](#).)

Although Parkinson's disease cannot be cured, it can be ameliorated, typically by drug therapy designed to increase the level of dopamine. Because the nigrostriatal pathways are damaged, dopaminergic pathways are underactive. To augment the level of dopamine, which cannot cross the blood-brain barrier, physicians give these patients a metabolic precursor of dopamine, [L-dopa](#). This precursor can reach the brain when taken orally, and can stimulate pre- and postsynaptic dopaminergic receptors. Monoamine oxidase (MOA-B) inhibitors are also given to reduce the breakdown of dopamine in the synapse and by glia (Connolly and Lang, [2014](#)).

Unfortunately, these drugs have numerous side effects. They may alter a person's mood, leading to euphoria or depression. Sometimes they interfere with memory and the ability to pay attention. In other cases, they lead to disorders in impulse control (such as binge eating, pathological gambling, hypersexuality, and compulsive shopping). In

extreme cases, an individual may even experience hallucinations and delusions. These effects tend to go away when the person stops taking the drug or when the dosage is reduced. Another unfortunate characteristic of these medicines is that they tend to lose effectiveness after a number of years (Olanow et al., [2009](#)).

Some experimental therapies for Parkinson's disease are being explored, but they are far from becoming standard treatment. One treatment, first examined in the 1990s, that received much attention is the grafting of fetal tissue rich in dopamine-producing cells to the striatum of an affected person. The strategy is for cells from the graft to produce dopamine and thus offset the loss of dopamine-producing cells in this region. Although initial results seemed promising, this procedure did not always result in amelioration of the disorder (Deierborg et al., [2008](#)), and, more troubling, sometimes had unintended consequences, including dyskinesias (i.e., unintended movement) and changes in cognition and mood. Because such brain transplants are irreversible (unlike medications, which can be discontinued), there are serious ethical considerations concerning how this potential therapy should be presented and discussed with patients (Duggan et al., [2009](#)). Although postmortem studies on the brains of people who have had such surgery revealed that the grafts do indeed take hold, they also showed evidence of pathological changes in these same nerve cells (see [Figure 4.22](#); Braak and Del Tredici, [2008](#)). For all the reasons just discussed, some researchers and clinicians question whether cell grafts will have long-term efficacy and become a viable treatment for Parkinson's disease. Nonetheless, interest in this potential therapy had been rekindled recently due to advances in understanding more about what type of patients may and may not benefit from such an intervention as well as new protocols for producing dopaminergic neurons from stem cells in large numbers and in a standardized way (Lindvall, [2016](#)).

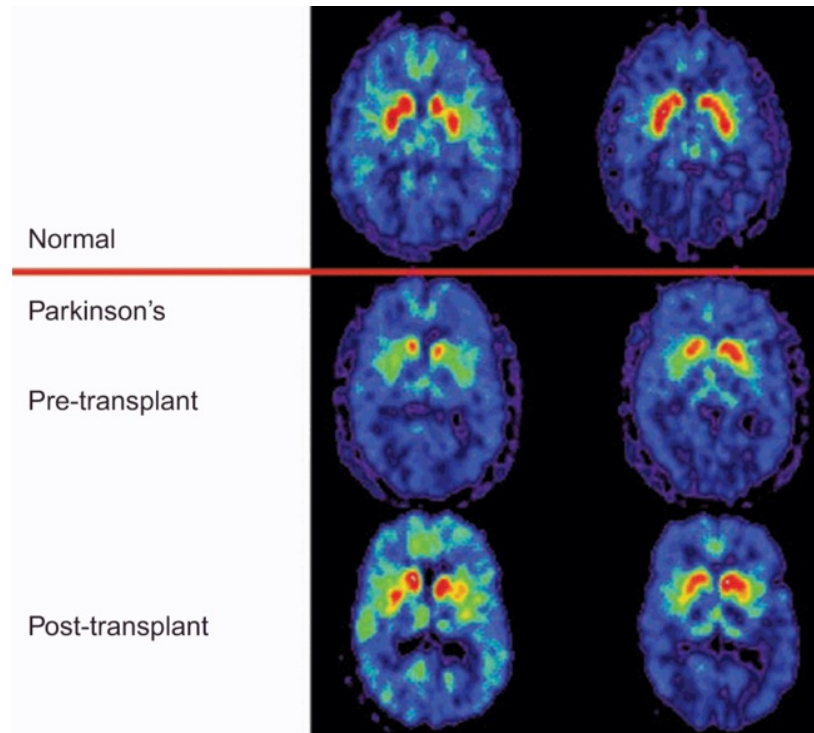


Figure 4.22 Fetal cell implants are used to treat Parkinson's.

Using a radioactive version of the dopamine precursor L-dopa as a tracer, researchers can evaluate the level of dopamine activity in the brain. These images compared a healthy participant (top) to a patient with Parkinson's disease both before and after treatment with fetal cell implants. Increased activity is indicated by red and yellow. Notice the increased activity in the basal ganglia in the post-transplant image.

Another approach to addressing bradykinesia and akinesia has been to ablate portions of the thalamus that are associated with tremor, in a procedure known as thalotomy; or to ablate the internal segment of the globus pallidus (GP_i), in a procedure known as pallidotomy. However, more recent approaches try to spare brain tissue and instead use [deep brain stimulation \(DBS\)](#), in which electrodes are implanted into the brain (rather than being placed on the surface) to stimulate tissue. This procedure involves chronically implanted electrodes that are used to artificially produce high-frequency stimulation in the subthalamic nuclei (which project in an inhibitory fashion to the GP_i). Typically, during the surgery the physician positions electrodes within the subthalamic nucleus and sends a mild current through them to determine the effect on motor behavior. In this manner, the physician can determine the site that produces the

best response in terms of reducing Parkinsonian symptoms with the fewest side effects. A pulse-generator implant is then used to provide continual and patterned input to the site (which can disrupt the bursting pattern, discussed earlier, that is often associated with Parkinson's). This method appears to be quite effective, although potential side effects include stimulation spreading to surrounding structures, negative neurocognitive changes, and the invasiveness of the procedures (Benabid et al., [2009](#)). Nonetheless, it appears to be more effective than standard treatments in terms of reducing the amount of time during which individuals exhibit troublesome symptoms, including motor disability and compromised activities of daily living (Schuepbach et al., [2013](#)). In addition, recent technological advancements, better understanding of which patients can best benefit from such an approach, as well as early intervention before cell loss is too great, appear poised to increase the effectiveness of such interventions (Rowland et al., [2016](#)).

Finally, there are indications that intensive training for certain compromised behaviors exhibited by Parkinson's patients can have wide-reaching effects. One procedure is designed to increase the volume, prosody, and intelligibility of vocal output, as well as increased bodily movements through multiple sessions per week over two or more months. This training has important effects on the lives of Parkinson's patients, as it fosters social communication with friends and family. In addition, the effects of such training appear to generalize, as they also lead to improvements in swallowing and increased facial expression (Fox et al., [2012](#)). Neuroimaging research suggests that the therapy works not by increasing activity in the basal ganglia, but rather by increasing activity in other brain regions, most notably motor, premotor, and dorsolateral regions of the frontal lobe that, at least to some degree, compensate for loss of function associated with the basal ganglia (Narayana et al., [2009](#)).

Huntington's Disease

An inherited neurologic disease associated with degeneration of the striatum (see [Figure 4.23](#)), **Huntington's disease** produces abnormal movements, cognitive deficits (eventually dementia), and psychiatric symptoms. We concentrate here on the motor aspects of Huntington's and leave a description of the intellectual and cognitive deficits for [Chapter 16](#). Huntington's disease is caused by an autosomal dominant gene, meaning that, although rare (1.6 cases per million), when the Huntington's gene is inherited, it always expresses itself. The Huntington's gene contains what can be considered a genetic "stutter": a sequence of repeating base pairs that varies in length. This genetic stutter leads to atrophy of the striatum, which usually manifests in earnest some time between the ages of 30 and 45 years when symptoms begin to become pronounced. The longer the repeating sequence, the greater the atrophy in the striatum, both in individuals who are not yet manifesting motor symptoms (Henley et al., [2009](#)) as well as those who are doing so (Jech et al., [2007](#)). Afterward, the disease involves a slow decline for 10 to 15 years and eventually leads to death.

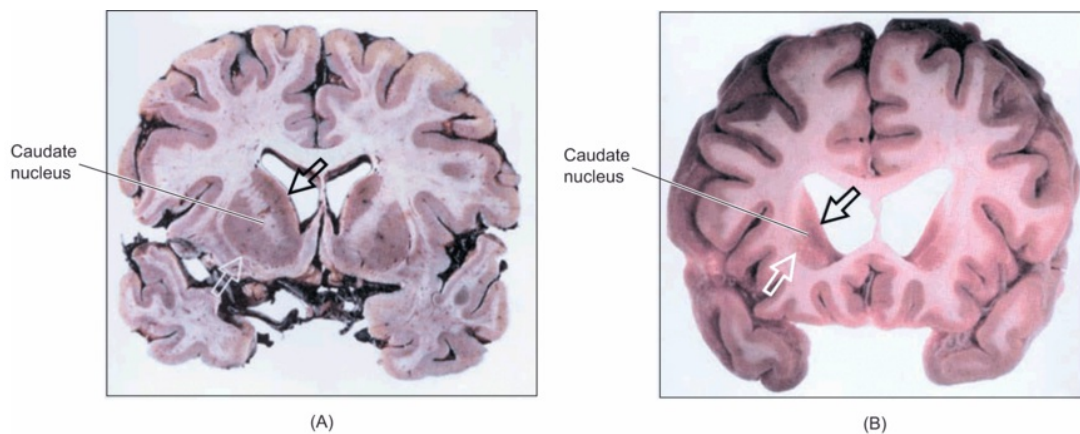


Figure 4.23 Huntington's disease causes degeneration of the caudate nucleus of the basal ganglia.

On the left (A) is the image of a healthy human brain; on the right (B) is a figure of someone with Huntington's. Notice that the caudate nucleus is much smaller than normal and that lateral ventricles have increased to take up the extra space in the individual with Huntington's disease.

(from De Souza and Leavitt, [2015](#))

The main motor symptom of Huntington's disease is [chorea](#), a variety of rapid, jerky movements that appear to be well coordinated but are performed involuntarily and ceaselessly in an irregular manner. Although people with Huntington's disease initially seem to be fidgeting, the movements eventually increase until they are almost incessant. They never involve just one muscle, but instead affect whole limbs or parts of a limb. Also present is [dystonia](#), which refers to slower movements caused by increased muscle tone and contractions that lead to abnormal posture, such as tilting of the head or arching of the back. Eventually, all movement becomes uncontrollable as the disease affects most of the body, including the head, face, trunk, and limbs. In the later stages, not only is the person unable to communicate through speaking or writing, but other basic movements required for independent living, such as walking and swallowing, are also lost (Ghosh and Tabrizi, [2015](#)).

Although chorea is considered the classic motor sign in Huntington's disease, individuals with this condition have additional motor difficulties. Some of these occur in the realm of initiation and execution of movement. For example, while neurologically intact individuals can use a cue to aid in performing a sequential button-pressing procedure, Huntington's patients are unable to use such advance information to initiate and execute movements. These other motor difficulties may be a marker for the disease because they may even precede the onset of chorea, the definitive motor symptom of the disorder (Bradshaw et al., [1992](#)). Other difficulties are manifested in learning a sequence of motor actions, which once again may precede the onset of full symptoms of the disease (Feigin et al., [2006](#)).

Arm movements are not the only aspect of motor control affected in Huntington's disease; the speed and initiation of voluntary eye movements are also affected. As we discussed earlier in this chapter, voluntary eye movements are under the control of frontal regions. These regions are likely to be affected in Huntington's disease because the basal ganglia, which are damaged, project to the frontal eye field. For example, when required to visually track a target that moves predictably between positions,

patients with the disease cannot direct their eyes to the correct location at the correct time. However, movements to an unexpected stimulus that appears in the periphery, which are under the control of the superior colliculus, a region unaffected in Huntington's disease, are normal (Tian et al., [1991](#)).

Brain imaging techniques provide insight into the progression of Huntington's disease. For example, the reduction in the size of the caudate has been linked to the severity of both motor and cognitive deficits (e.g., Starkstein et al., [1988](#)). Even more notable, the size of the striatum in individuals who are carriers of the Huntington's gene but not yet exhibiting motor symptoms is a predictor of disease onset, up to 15 years prior to diagnosis (Paulsen et al., [2008](#)). These studies also highlight the fact that although atrophy is most pronounced in the striatum, atrophy is observed in other brain regions as well, including the thalamus, cingulate cortex, and premotor cortex, among other regions (Douaud et al., [2006](#)). Moreover, the particular set of structures affected may influence the specific set of symptoms that are observed in any given individual (Waldvogel et al., [2012](#)). Huntington's disease causes a slow decline to death because there is no treatment or cure. However, drugs that deplete or block dopaminergic transmission are often given to aid in reducing the severity of the motor symptoms (Phillips et al., [2008](#)).

Currently, researchers are trying to learn more from people with Huntington's disease about the multiple ways in which the learning of motor sequences and acts can be performed by the brain. Because these individuals have disrupted cortico-striatal pathways, acquisition must rely on other systems, such as cortico-cerebellar motor pathways (Doyon, [2008](#)). In fact, recent neuroimaging studies have shown differential reliance on thalamo-cortical pathways in presymptomatic individuals with Huntington's disease who are learning motor tasks (Feigin et al., [2006](#)). Studies such as these reveal the variety and complexity of the ways in which motor actions and processes can be implemented by the brain.

Tourette's Syndrome

This relatively rare disorder manifests itself as a variety of vocal and motor [tics](#), which are repetitive involuntary movements of a compulsive nature that wax and wane in severity. Tourette's syndrome can vary in severity from a few tics that occur only when the person is tired or tense to between 30 and 100 tics per minute. Unlike the other motor disorders discussed so far, all of which affect people in their middle to late adult years, Tourette's syndrome manifests in childhood, usually before the age of 11 years (for a review covering all aspects of this disorder, see Ganos et al., [2013](#)).

Tics can take various forms. Simple motor tics, usually present by age 6 or 7, involve just one portion of the body, such as repetitive blinking of the eyes, twitching of the nose, or shrugging of the shoulders. More complex tics involve several muscle groups and seem to be more purposeful. These can include complex hand gestures, or repetitive touching of people or objects. Although the tics typically involve the face and head, the limbs and even the entire body may be affected. For example, movements akin to those seen in pogo dancing or the head banging of punk rockers can be observed (Hoekstra et al., [2009](#)). Vocal tics are usually observed a bit later, but they too can be simple or complex. Simple tics usually involve actions like throat clearing or sniffing, whereas more complex ones can include [echolalia](#), the repeating of what has just been said, and coprolalia, obscene speech. Because of the unusual behavior of these children, they are often misdiagnosed as having psychiatric disorders.

Because these motor tics occur involuntarily, repetitively, and in a stereotyped manner, Tourette's syndrome has long been thought to involve dysfunction of subcortical motor regions (rather than cortical motor regions, which are more involved in voluntary movement). Although neither a definitive neural substrate nor cause has been isolated, a variety of evidence points to dysfunction of the basal ganglia and the associated cortical-striatal-thalamic-cortical brain circuitry (refer back to [Figure 4.8](#)), with alterations of both dopaminergic and GABAergic function.

Because tics are executed in a stereotyped habitual manner, they may represent an inappropriate form of habit learning. As we discussed earlier in the chapter, dopamine

is thought to be involved in the creation of habit-like behaviors, and not surprisingly the tics of Tourette's syndrome are reduced by treatment with agents that block or reduce D₂ dopamine receptors (Hartmann and Worbe, [2013](#)). In addition, there is also evidence of disrupted GABAergic function, which compromises the ability to inhibit such actions. Consistent with this idea, single-cell recordings in the internal segment of the globus pallidus of individuals about to undergo neurosurgery showed that about half of them exhibited activity that was synchronous with the performance of tic (Zhuang et al., [2009](#)). In addition, neuroimaging studies reveal reduced volume of the caudate in individuals with Tourette's syndrome and such volume reductions predict the severity of tics (e.g., Peterson et al., [2003](#)). Also associated with the severity of tic production is alteration in the white-matter characteristics of cortical-striatal-thalamic-cortical loops.

Finally, the type of tic a given individual manifests may depend on which of the distinct cortico-striatal-thalamo-cortical circuits is affected (refer back to [Figure 4.8](#)). For example, facial tics may reflect a failure of circuits that include ventromedial areas of the caudate and putamen, which receive projections from portions of the motor and premotor regions that control orofacial movements. Similarly, vocalizations that are profane in nature may involve the limbic loop as well as the motor loops (Mink, [2001](#)). The ability to control the tics, which usually improves during adolescence, may involve the recruitment of additional brain regions, such as the SMC, and involves changes in myelination and functional connectivity of cortical-striatal-thalamic-cortical loops (for review, Jackson et al., [2015](#)).

The tics of Tourette's differ from the movements observed in Huntington's disease, in that not only are they specific to a part of the body, but they also have an associated motivational or emotional component. Tics occur with greater frequency during times of emotional arousal or upset, when a person is anxious, excited, or fatigued. Furthermore, many individuals have a premonition before the tic, which feels like an urge, tension, impulse, itch, or something of that nature. Once the tic is emitted, this feeling

disappears, leading to relief. Similar to compulsive behaviors, in which anxiety about a certain item (e.g., germs) is relieved by an action (e.g., hand washing) (see [Chapter 14](#)), people with Tourette's syndrome claim that the more they try to suppress a tic, the greater their compulsion to produce it. In fact, half or more of people with Tourette's exhibit some aspects of obsessive-compulsive disorder. In addition, in individuals with Tourette's, there is an increased incidence of attention-deficit/hyperactivity disorder, which may also involve dysregulation of systems involving motivation and reward (see [Chapter 15](#)).

While the proximate cause of Tourette's syndrome may be basal ganglia dysfunction, the overarching cause remains unclear. Much work suggests that there is a genetic component, as the disorder appears to run in families. But at present, there is no one clear mechanism of genetic transmission and there may be multiple susceptibility factors that lead to the disorder. Given that the disorder is about four times more prevalent in males than females, some researchers have suggested that it may be caused by an alteration in androgenic steroids during fetal development. In addition, recent research has centered on investigating whether there is an alteration of autoimmune mechanisms (mechanisms in which the body mistakenly treats portions of itself as if they were pathogens or invaders to be destroyed) as a result of infection or environmental effects, such as maternal smoking during pregnancy (Paschou, [2013](#)). Although the underlying cause of Tourette's syndrome remains elusive, dysfunction of the basal ganglia and its associated cortical loops are highly implicated.

Cortical Motor Disorders

As we have learned, most subcortical motor disorders manifest as slowness of movement or as an increase in movements. Cortical motor disorders have a different effect, tending to disrupt the ability to pursue specific plans of motor action or to relate motor action to meaning. Next we discuss a family of such disorders, the apraxias.

Apraxia is an inability to perform skilled, sequential, purposeful movement that cannot be accounted for by disruptions in more basic motor processes such as muscle weakness, abnormal posture or tone, or movement disorders (such as tremors or chorea) acquired as a result of brain damage. It is commonly observed after stroke, traumatic brain injury, and in people with neurodegenerative disorders. Apraxia is more often observed after damage to the left hemisphere, although, as we discuss later, the type of apraxia varies depending on the exact region of the brain that is damaged.

Two main pieces of evidence suggest that apraxia is a higher-order motor deficit rather than a deficit associated with lower-level aspects of motor control. First, apraxia usually exhibits itself bilaterally. If the deficit were at a low level and concerned the control of specific muscles, it would be expected to be observed only for the limbs contralateral to the site of damage. Second, low-level motor processes, such as the ability to grasp objects with adequate force, are mostly intact in patients with apraxia.

Dichotomous Classifications of Apraxia

Apraxia can take many forms, and there is ongoing debate as to how to classify them (see Petreska et al., [2007](#)). A classic way of distinguishing between types of apraxia was introduced in [1905](#) by Liepmann, who differentiated between ideational and ideomotor apraxia. He suggested that **ideational apraxia** (sometimes also called conceptual apraxia) impairs the ability to form an “idea” or mental image of the intended movement, precluding the person from determining which actions are necessary and in what order they should occur. For example, a person with ideational apraxia might be unable to light a candle because she might not be able to sequence the necessary events (e.g., tear a match out of a matchbook, close the matchbook cover, strike the match against the cover, bring the match to the candle’s wick).

Liepmann suggested that even if such a mental image of the intended movement were intact, difficulties might also arise from a disconnection between the idea of the movement and its execution, a disorder he called **ideomotor apraxia**. He reasoned that the impact of such a disconnection would be most pronounced for motor actions that

were the least concrete, not driven by interactions with external objects, and required memory, such as gestures, meaningless movements, or movements that had to be imitated. In contrast, the production of most everyday motor actions would be relatively undisturbed. Unlike patients with ideational apraxia, these patients would be able to sequence complex movements, although the constituent acts would be disrupted.

Since this original conceptualization, there have been decades of debate around the definition of these disorders, and whether they indeed represent two separate syndromes. Some theorists have suggested that ideational apraxia might be just a more severe version of ideomotor apraxia (Zangwill, [1960](#)). Others argue that ideational apraxia is characterized by an inability to use an actual object, such as a hammer, a toothbrush, or a pair of scissors, which are considered transitive gestures since they act on an object. This syndrome is distinguished from ideomotor apraxia in which the cardinal symptom is an inability to perform or imitate gestures, such as making the sign of the cross or saluting, that are conceptual in nature and that do not act upon an object. These are sometimes called intransitive gestures, because, like intransitive verbs, they do not have an object upon which they act (De Renzi et al., [1968](#)).

Still another conceptualization proposes that some apraxias lead to the loss of “visuokinesthetic motor” memories, which contain not only information about the selection and production of specific gestural actions, but also linkages to information about the visual and kinesthetic feedback that will occur during performance of the motor act (Heilman and Rothi, [1985](#)). Damage to parietal regions that are thought to store their memories results in apraxia in which a person can neither perform gestures correctly nor discriminate between them (e.g., knowing the difference between the gesture for brushing one’s teeth and that for flipping a coin). If this parietal region is intact but damage disconnects it from motor centers in the frontal cortex, the person will be able to discriminate between correctly and incorrectly performed gestures made by others (because the stored program is intact) but will not be able to produce correct gestures (because the stored program cannot reach motor areas) (Heilman et al., [1982](#)).

As should be obvious, researchers have not yet formed a clear consensus on how to

divide the apraxias into meaningful subtypes. Because of the difficulties in distinguishing between types of apraxias on theoretical grounds, some researchers instead categorize them on descriptive grounds. Thus, rather than talking about ideational versus ideomotor apraxia (which may mean different things to different people), some researchers use descriptive terms such as “apraxias of symbolic actions” or “apraxias of object utilization” (e.g., Dee et al., [1970](#)). Another approach taken to understanding the apraxias is to determine what type of information (sensory, conceptual, memorial) cannot be linked with motor output (e.g., Westwood et al., [2001](#); Heath et al., [2001](#)).

Finally, others classify apraxia by reference to the part of the body that is affected. If facial movements are disordered, the condition is known as **[oral \(buccofacial\) apraxia](#)**. This disorder is associated with difficulty in performing voluntary movements with the muscles of the tongue, lips, cheek, and larynx, such as sticking out the tongue, clearing the throat, blowing a kiss, and yawning. These difficulties may also extend to oral movements used to manipulate or act upon objects, such as blowing out a match or sucking on a straw. **[Limb apraxia](#)**, in contrast, disrupts the ability to use the limbs to manipulate items such as screwdrivers, scissors, and hammers (e.g., De Renzi and Lucchelli, [1988](#)), as well as more complex series of movements, such as opening a can of soup or opening a door with a key (e.g., Poeck and Lehmkuhl, [1980](#)).

Limb apraxia also affects the ability to use movements in a symbolic way, as in gestures like waving goodbye or saluting, and in pantomime (e.g., Heilman and Rothi, [1985](#)). In pantomime, individuals affected with this type of apraxia commonly use a body part to represent the object that they would be manipulating. For example, if asked to imitate putting a spoonful of sugar into a cup of coffee and then stirring it, an individual with limb apraxia will extend the index finger below the others, as if to represent the spoon, and will move it around in a circular manner rather than rotating the wrist as would occur in a correct pantomime (see [Figure 4.24](#)). Their performance tends to be better when they actually perform the task, presumably because of the visual and tactile-kinesthetic cues they receive under those conditions.

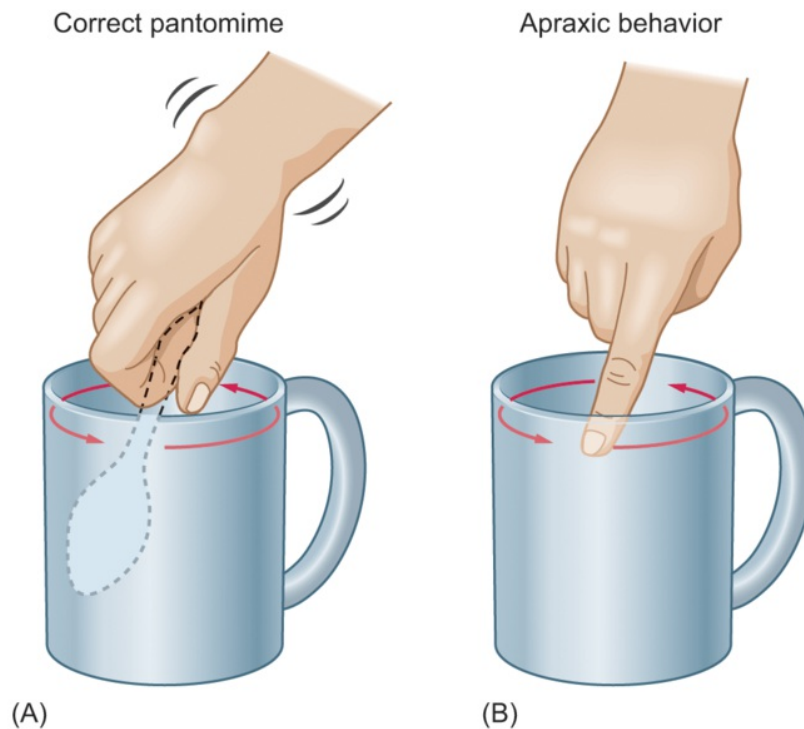


Figure 4.24 Example of apraxic behavior.

When attempting to pantomime, an individual with apraxia often uses a limb to represent an object.

Regardless of how they are characterized, apraxias can lead to severe difficulties in everyday life. For example, individuals with apraxia may have difficulty making a cup of coffee or eating a meal. Simple tasks like brushing one's teeth or shaving may be impossible, and indeed quite dangerous if the wrong tool or action is selected (e.g., using a razor as a toothbrush). In fact, it has been suggested that caretaking for someone with apraxia is more demanding than caretaking for someone with hemiparesis (Foundas, [2013](#)).

Lesions That Lead to Apraxia

As you might expect, there is also no agreement on the lesion location that leads to apraxic behavior. In fact, apraxia can be observed after damage to a large variety of regions, although it is most typically observed after parietal or frontal lesions of the left hemisphere, consistent with activation of these regions during the pantomime of object

use (Niessen et al., [2014](#)). What can be said with some certainty is that the conception, planning, and production of skilled movement, often referred to as [praxis](#), probably requires a set of brain structures spanning a wide variety of brain regions, including the parietal, prefrontal, motor, and subcortical regions, each contributing in a different manner to the planning, retrieval, and/or implementation of motor action plans (Gross and Grossman, [2008](#)). Depending on the specifics of the motor task, some of these regions may be more involved than others, and the configuration in which they are employed may vary. For example, learning to play a tune on the piano, which does not rely so much on visual feedback, may tax different portions of the praxis system than learning to juggle, which requires much more eye–hand coordination. Likewise, giving a salute may require retrieving the kinesthetic and spatial information associated with that action for someone who does not do it often, but may rely on more automatic (and thus subcortical) regions for someone in the military who performs that action habitually. As such, it is not surprising that different varieties of apraxic disorder do not map neatly onto particular regions of brain tissue.

Other Varieties of Apraxia

There are other syndromes, that while referred to as apraxia because a person has difficulty performing complex motor acts, appear to arise primarily from difficulty in spatial processing. Two examples of such syndromes are constructional apraxia and dressing apraxia. In [constructional apraxia](#), items cannot be correctly manipulated with regard to their spatial relations. For example, wooden blocks cannot be manipulated to copy an arrangement created by someone else. In [dressing apraxia](#), the affected individual has difficulty manipulating and orienting both clothes and his or her limbs so that clothes can be put on correctly (e.g., opening a jacket so that the arm can be inserted, and properly putting an arm out and bending it at the elbow to put on the jacket). These syndromes are generally observed after right-hemisphere lesions and are often associated with spatial processing difficulties and hemineglect. Many

neuropsychologists do not consider these apraxias per se, but rather motor manifestations of visuoconstructive disorders.

Still other apraxias result from a disconnection syndrome rather than from difficulties in motor programming. We have already discussed the idea that in certain cases of apraxia, visuokinesthetic programs may not reach motor areas because of a disconnection between parietal and frontal areas. Another type of apraxia that results from a disconnection syndrome is [callosal apraxia](#), which is characterized by an inability to perform a skilled motor act with the left hand in response to a verbal command. This disorder is characterized by damage to the corpus callosum, and the explanation for the observed difficulty is as follows (Rubens et al., [1977](#)). The left hemisphere can interpret the verbal command and relays that information to left parietal regions so that the appropriate motor program can be assembled. Once formed, the motor command is forwarded to the premotor and motor cortices of the left hemisphere, which allow the action to be performed by the right hand. However, due to the callosal disconnection, those motor programs are trapped in the left hemisphere. They have no way of reaching the right hemisphere, which controls the left hand, and as such the left hand is apraxic. [Figure 4.25](#) diagrams the essential anatomical relations of this syndrome.

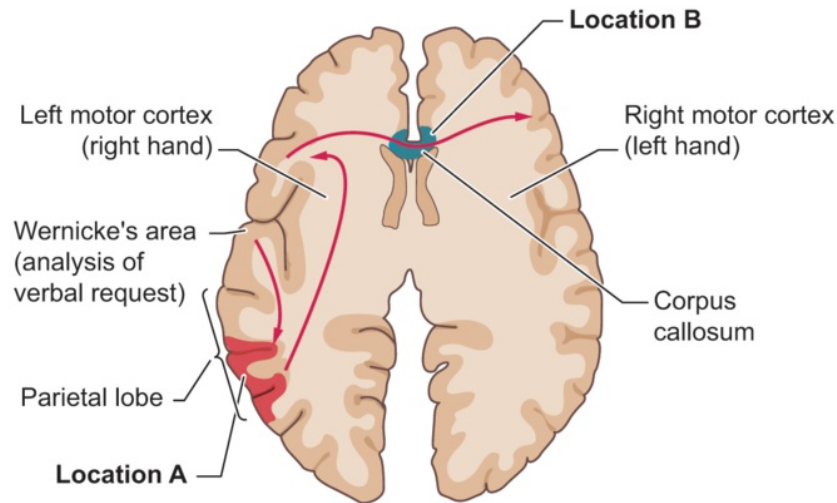


Figure 4.25 Anatomical mechanisms of unilateral and bilateral apraxia.

Wernicke's area analyzes a verbal request and transmits this information to the left parietal region (Location A), where the correct movements are selected. If this region is damaged, bilateral apraxia results. In contrast, in unilateral apraxia of the left hand, the left parietal region is intact, so information about the correct movements is sent forward to the left motor cortex, where the motor commands are executed. Hence, the right hand is not apraxic. However, because of a lesion of the corpus callosum (Location B), the information cannot be relayed to the right hemisphere and apraxia of the left hand results.

As we have learned in this chapter, the control of action occurs because of activity across a variety of structures in the brain. So perhaps next time you go to sit down and type that next term paper on your computer, you can better appreciate how your brain accomplishes such a task. You'll perhaps now be aware that it is your cortex that takes the intention of the words you wish to type and translates them into concrete motor plans. And you'll recognize that, based on their tuning by experience, your subcortical and cerebellar regions allow you to type relatively quickly and fluently, even if you are a two-finger typist!

Summary

Brain Structures Involved in Motor Control

- Motor tracts transmit information from the brain to muscles.
- The cerebellum is important for the smooth coordination of movements, rapid movements that must be planned with little chance for feedback, and the learning of motor skills. It is thought to create a forward model that helps to predict the sensory consequences of a motor plan.
- Via its connections through a series of loops through the thalamus and up into the cortex, the basal ganglia can modulate the initiation and cessation of movements. They also play a role in motor planning and learning.
- Primary motor cortex generates movement most likely by controlling the force or other parameters of muscle movement.
- The supplementary motor complex is thought to be involved in specifying, preparing, and initiating a motor plan for an action, which is an abstract representation of an intended movement that is preprogrammed before the motor act is initiated.
- Premotor regions are thought to specify the type of motor action (such as a grasp) that is necessary to perform a task. A portion of the premotor area, known as the frontal eye field, programs voluntary eye movements such as those involved in scanning visual space.
- The anterior cingulate cortex plays an important role in the selection of motor responses, especially when they are novel or atypical. It also plays a role in the evaluation of the outcome of such movements, such as whether or not they lead to an error.
- The right inferior frontal cortex has been suggested to play a specific role in the inhibition of motor responses.
- The parietal lobe links movements with sensory information, including visual, proprioceptive, and kinesthetic information. It is thought to estimate what motor

actions are required to meet a particular end state, and can aid in the on-line modulation of actions. It is also important for linking motoric actions to their conceptual significance, such as occurs when saluting or making the sign of the cross.

- Complex action requires the coordinated effort of all these regions in an integrated manner.

Motor Disorders

- Subcortical motor disorders affect the form and timing of movements, whereas cortical motor disorders affect the conceptual clarity of motor acts, either by disrupting the sequencing of complex motor acts or by disrupting the ability to have a motor act represent a concept.
- Parkinson's disease, which occurs because the putamen does not receive dopaminergic input due to the death of cells in the substantia nigra, results in an inability to initiate (akinesia) or slowness of spontaneous movement (bradykinesia), rhythmic oscillating movements (tremors), rigidity of movement (cogwheel rigidity), and disturbances of posture.
- Huntington's disease, which occurs because of damage to the striatum, results in involuntary, undesired jerking and writhing movements.
- Tourette's syndrome, a rare disorder that manifests itself in childhood, is characterized in less severe cases by tics and twitching of the face, the limbs, and other regions of the body. In more severe cases, the patient makes vocalizations such as cries, grunts, and curses.
- Apraxia is a disorder that typically results from left inferior parietal lesions or left frontal lesions and prevents the individual from performing sequential skilled motor acts.

- There are many competing classifications of apraxic disorders. Some emphasize the body part that is affected, others emphasize the difference between movements required to use objects as compared with those that have symbolic significance, and still others emphasize whether the idea of movement is lost or whether such ideas are intact but disconnected from the movements required to implement them.
- There are other disorders that interfere with movements but that are not true apraxias because they mainly involve deficits in visuospatial processing. In constructional apraxia items cannot be correctly manipulated with regard to their spatial relations; while in dressing apraxia, the limbs and clothes cannot be manipulated so as to dress.
- Callosal apraxia is a disconnection syndrome characterized by an ability to perform movements or manipulate objects with the left hand in response to verbal commands due to a lesion of the corpus callosum.

Chapter 5

Sensation and Perception



The Retina

Photoreceptors

Ganglion Cells

Receptive Fields

Receptive Fields of Retinal Cells

Center-Surround Receptive Fields

Pathways From the Retina to the Brain

The Tectopulvinar Pathway

The Geniculostriate Pathway

Lateral Geniculate Nucleus

Layers of the LGN

Retinotopic Mapping in the LGN

Feedback Connections to the LGN

Primary Visual Cortex (Striate Cortex)

Organization of Striate Cortex

Binocular Integration in Striate Cortex

Contextual Modulation of Cells in Striate Cortex

In Focus: Seeing What's Not There: Visual Illusions and the Striate Cortex

Visual Areas Beyond the Striate Cortex

Multiple Maps of the Visual World

[Area V4: A Special Module for Coding Color?](#)

[Blindsight and the Visual Pathways](#)

[Divergence into the “What” and “Where” Pathways](#)

[Auditory Processing](#)

[Computational Problems in Audition](#)

[Organization of the Auditory Pathways](#)

[Brainstem Computation of Spatial Location](#)

[Organization of Auditory Cortex](#)

[Auditory-Visual Interactions](#)

[Conclusions](#)

[Summary](#)

During a serious car accident, Ron received a blow to the back of his head on the right side. As a result of damage to his right visual cortex, he became completely blind to all objects in his left visual field, often bumping into things on his left. Yet, because the damage was restricted to visual cortex, he processes all other information normally, such as sounds coming from his left side or objects felt with his left hand.

After his accident, Ron visited a researcher who wanted to carefully determine what Ron could and couldn't see. The researcher flashed a light at many different locations on a screen and asked Ron to indicate when he saw it. Ron had no problem seeing the light whenever it fell in his right visual field. However, when a light was flashed in the left visual field, and the tester asked, “Do you see anything there?” Ron's response was always: “No, sorry, I don't see anything.” It didn't matter whether Ron had both eyes open or was viewing the screen with just one eye; he always reported not seeing anything in the left half of space.

Despite Ron's insistence that he was blind to everything on the left, the examiner prodded Ron to answer questions anyway. First, the examiner told Ron

that he would be shown a small square within the left visual field; Ron should decide whether it was moving up or down. “But I can’t see anything!” Ron responded with some exasperation. “Well, OK, but just go ahead and guess on each trial anyway,” replied the examiner. Ron complied. Next the examiner told Ron that for the next set of trials, he should decide whether an object in the left visual field was colored or gray. Ron thought to himself, “This is pretty stupid, since I don’t see anything,” but he guessed anyway. For the next set of trials, the examiner asked whether a line presented in the left field was oriented vertically or horizontally. Finally, for the last set of trials (which Ron thought was utterly ridiculous), the researcher asked him to point to the location in his “blind” visual field where he thought an object might be. At the end of the session, Ron said, “I’m not exactly sure what all this was about, because, as I told you, I can’t see anything.”

“This may surprise you, Ron,” the researcher replied, “but actually you guessed correctly more often than not!”

The man you have just read about exhibits a phenomenon known as [blindsight](#), which involves the retention of some visual capabilities without the conscious experience of seeing (Weiskrantz, [2009](#)). What makes cases such as these so fascinating is that they raise a fundamental question: What does it really mean to “see”?

When you open your eyes in the morning, the visual world appears to you, seemingly without any effort. The immediacy and apparent ease of visual awareness makes it hard to believe that a large proportion of your brain is working very hard to solve the complex problems of vision. In the brains of humans and other primates, visual processing is highly developed, with the neural machinery that supports vision taking up a large proportion of cortex. The immense amount of brain tissue dedicated to sight enables us to have the exquisitely detailed color vision that is one of the hallmarks of being a primate.

The topic of sensation and perception is so complex that it cannot be covered adequately within a single chapter. It's first important to appreciate that researchers often use the terms sensation and perception to mean different things. The term sensation is usually used to describe the registration and initial encoding of sensory information, such as light, sound waves, pressure, and so forth. The term perception is usually used to refer to how the brain organizes sensory information into meaningful representations of objects and scenes, such as visual objects or recognizable sounds. For example, sensation can allow our eyes to register light of different wavelengths and different spatial locations at different points in time, while perception integrates those building blocks and constructs a mental representation, let's say an image of a butterfly landing on a flower. Although most of our focus in cognitive neuroscience is on the higher-level processes of perception, understanding the initial steps of sensation can help us to better appreciate how perceptions are created.

The first part of this chapter gives an overview of the basic elements of the visual system, following information as it enters the eye and ascends through various steps until it reaches the cortex. As you will learn, there are two main visual processing pathways once visual information reaches the cerebral cortex. One of these pathways, discussed in [Chapter 6](#), is important in recognizing the identity of objects; the other path is important in locating objects in space, and is covered in [Chapter 7](#). Both the recognition of objects and the correct localization of objects in space require basic information – such as the presence of different wavelengths of light in various locations – to be first registered, coded, and organized by the brain. Those more fundamental processes are reviewed in this chapter. Together, these three chapters should help you to appreciate the astonishing computations that go into your everyday experience of seeing, and will also help you to understand the many different ways in which visual perception can go awry.

Although vision is especially well developed in primates, auditory perception (hearing) is also paramount. The second part of this chapter reviews the fundamentals of

the auditory system, with an emphasis on similarities and differences between visual and auditory processing. Although space does not permit a discussion of the other three senses (touch, smell, and taste), [Chapter 1](#) provides a brief overview of the regions that are involved in these senses as well as audition and vision.

Throughout our discussion of the many steps of sensory and perceptual processing, you will notice a theme emerging: namely, that the brain deals with the complexities of perception by breaking the problem down into parts, with different systems tackling different aspects of perception. We can see this pattern – which we call parallel processing – at every level of the visual system, beginning with the retina in the eye and extending through the higher levels of the cortex that are dedicated to processing visual information. Parallel processing is evident in the auditory system as well. Toward the end of this chapter, we will also learn about how information from different senses, such as vision and hearing, are integrated.

The Retina

The [retina](#) consists of several layers of cells at the back of the eye that register light and begin the initial steps of representing the visual world (see [Figure 5.1](#)). The retina is really an extension of the brain. Retinal tissue is derived from neural tissue during embryological development, and the retina acts as an information processor, much like the rest of the brain. We tend to think of the eye as merely registering light and sending that information to the brain, but computations actually go on within the retina itself, so that the brain receives information that has already been partly digested and transformed (for more details about the retina, see Werner and Chalupa, [2014](#)).

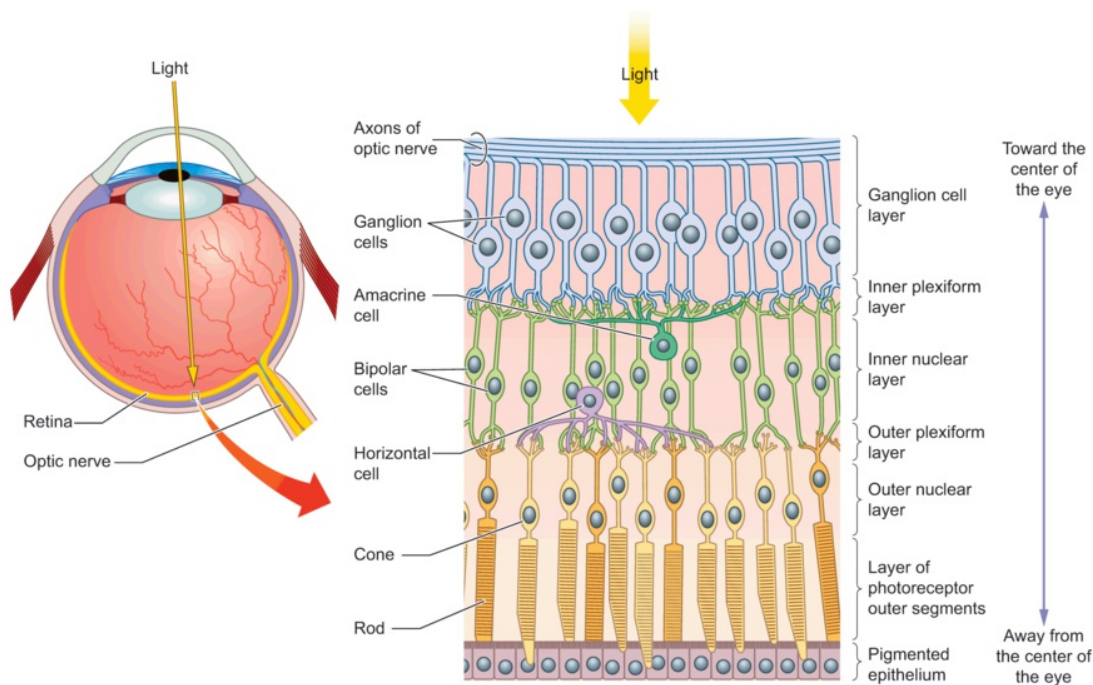


Figure 5.1 The structure of the retina.

Photoreceptors

Parallel processing begins in the retina with the division of the sensory receptors into rods and cones, which are collectively known as **photoreceptor** cells (see [Figure 5.2](#)). There are approximately 120 million rods and 6 million cones in the human eye. Both rods and cones contain pigments that absorb light. When photons of light are absorbed, a cascade of chemical changes occurs inside the rod or cone, which in turn leads to changes in membrane polarization and the release of neurotransmitters, signaling to the next layer of cells within the eye. Therefore, rods and cones take light energy and transform it into the electrochemical energy used in the nervous system.

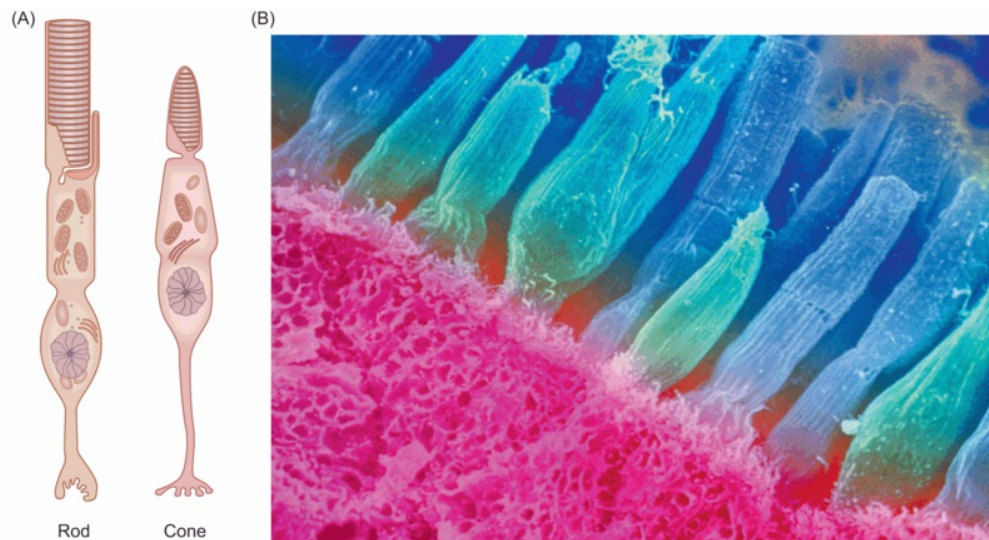


Figure 5.2 Rods and cones in the retina.

(A) Diagram of a rod and a cone photoreceptor. (B) Photograph of rods and cones from an electron microscope.

Source: Omikron Photo Researchers Inc.

The rods and cones differ in three main ways. First, they contain different pigments, which makes their response to light distinct. The rods contain just one pigment, called rhodopsin, which is sensitive to very small amounts of light. In broad daylight, this pigment becomes saturated and the rod system no longer functions. At that time, processing is taken over by the cones. There are three different types of cones, each containing a different pigment. The three types of cone pigment are sensitive to wavelengths in different portions of the light spectrum: short wavelength, which we perceive as blue; medium wavelength, which we perceive as green; and long wavelength, which we perceive as red. The specific pattern of activity across these three types of receptors ultimately enables the exquisite variation in colors that we can perceive.

Second, the rods and cones also differ in their distribution across the retina. Cones are packed more densely in the center of the retina, a region known as the [fovea](#), whereas rods are located more in the periphery. When you fixate your gaze on a point in space, light from that point falls upon the fovea, and is processed by the dense

population of cones there. Finally, rods and cones are hooked up to the retina's output layer of cells, called [ganglion cells](#), in somewhat different ways. Many rods feed into each ganglion cell, whereas only a few cones feed into each ganglion cell.

The differences in how rods and cones are wired up to other cells is partly what gives the rod and cone systems different properties. Because many neighboring rods send their input to one ganglion cell (via intermediate cell layers), low levels of light registered by many rods can summate and cause a response in the ganglion cell. This feature, together with the supersensitivity of rhodopsin to tiny amounts of light, allows the rod system to be more useful under low light levels, such as at night. However, there is a trade-off for the rod system: It is less sensitive to fine details. Because so many rods feed into one ganglion cell, information about the precise location of the light is lost.

In contrast, only a few cones send input to each ganglion cell. By having less summation across multiple photoreceptors, the cone system preserves more fine-grained information about where on the retina light has been detected. The trade-off for the cone system, however, is that it cannot function under low light conditions, because the summation of information from the cones is not sufficient to make a ganglion cell fire. Thus, the rod and cone systems have cleverly evolved to serve different aspects of vision.

To see the difference between the rod system and the cone system, try going outside at night and looking up in the sky. Find a dim star somewhat in the periphery of your vision, and then look at it directly. You should notice that you can see the star if you look slightly away from it, but it disappears when you try to focus directly on it. Given what you have learned about the rod and cone systems, can you explain why this happens?

Consider that the rod system is especially sensitive to low light levels, but that rods tend to be distributed away from the center of the retina. When you look slightly away from that dim star, its light is falling on the periphery of the retina where the rod system dominates. However, when you look directly at it, the dim starlight is falling on your fovea, where the cone system dominates. Although individual cones might still be

responsive to that dim light, these cones do not summate as much as rods do, so the signal is lost. This example illustrates one of the differences between rods and cones, and also reminds us that what we perceive is completely dependent on the organization of our visual system to register and process that sensory information.

Ganglion Cells

Whereas the rods and cones are the “input” part of the retina, the ganglion cells are the “output,” sending information along from the eye to the brain. As you can see in [Figure 5.1](#), there are actually several layers of cells in-between the photoreceptors on the surface of the retina and the ganglion cells, but space does not permit us to examine their operations in detail. The ganglion cell bodies are located in the retina, and their axons stretch out from the retina toward the brain, forming the optic nerve.

Retinal ganglion cells come in two main types, again illustrating the concept of parallel processing in the visual system. The two main types of ganglion cells are called M cells and P cells, which stand for magnocellular (large) and parvocellular (small) types, respectively (see Roska and Meister, [2014](#), for review). These two types of cells form functional pathways with similarly named cells in the thalamus. The M ganglion cells tend to be responsive to coarse patterns, and they are tuned to detect rapid motion, a feature that likely derives from how they are wired to subsets of intermediate cells in the retina (see Demb, [2007](#); Masland, [2004](#)). P cells, in contrast, preserve color information that is coded by the cone system. As we will see, M and P cells send their output to different destinations within the brain.

Although we have described the ganglion cells as if there were only two main types, in fact the situation is much more complex. The [M and P ganglion cells](#) are the best-characterized types, and they constitute about 80% of all ganglion cells. However, there are as many as 20 distinct types of ganglion cells, all of which are distributed across the retina in mosaic patterns (Roska and Meister, [2014](#)). Some ganglion cells even contain a pigment molecule that is sensitive to light, contradicting the long-held assumption that only rods and cones contain light-absorbing pigments. Researchers currently believe

that the pigment-containing ganglion cells contribute to “nonvisual” aspects of responding to light, such as the entrainment of the body’s circadian (daily) rhythms to external light sources (Berson, [2014](#); Schmidt et al., [2011](#)).

One additional type of ganglion cell is the so-called small bistratified type, which has a unique projection to the thalamus, as we will see in a later section. These small bistratified cells appear to carry some color information, especially pertaining to blue and yellow. Each of the remaining ganglion cell types is anatomically distinct, but their functional differences are not currently well understood (Sanes and Masland, [2015](#)). The presence of so many distinct ganglion cell types is an indication of the enormous complexity of processing that occurs before visual information even exits the eye.

Receptive Fields

Before we leave the retina, there is one more property of cells in the visual system that is important to understand. Every cell in the visual system – whether a photoreceptor, ganglion cell, or cell higher up in the visual pathway – has a property known as its receptive field. The [receptive field](#) refers to that specific region of visual space to which a particular cell responds. That is, each cell only cares about patterns of light in a particular spatial location and is essentially “blind” to light outside of that area. Remember that the receptive field is not a part of the cell. Rather, it is a part of visual space in which light will affect the cell’s firing rate.

Receptive Fields of Retinal Cells

Receptive fields are easiest to understand by starting at the level of the photoreceptors. Light must be absorbed by a particular rod or cone for that photoreceptor to respond. When the eye is stationary, light from a particular location in space will only fall on a particular part of the retinal surface, and therefore will only stimulate specific subgroups of rods or cones.

Next, consider the receptive fields of retinal ganglion cells. Remember that ganglion cells receive inputs from specific sets of rods or cones. Thus, an individual ganglion cell will only respond to light from a particular area of space – the specific area of space to which the rods and cones that feed into that particular ganglion cell are sensitive. That area of space is the ganglion cell's receptive field.

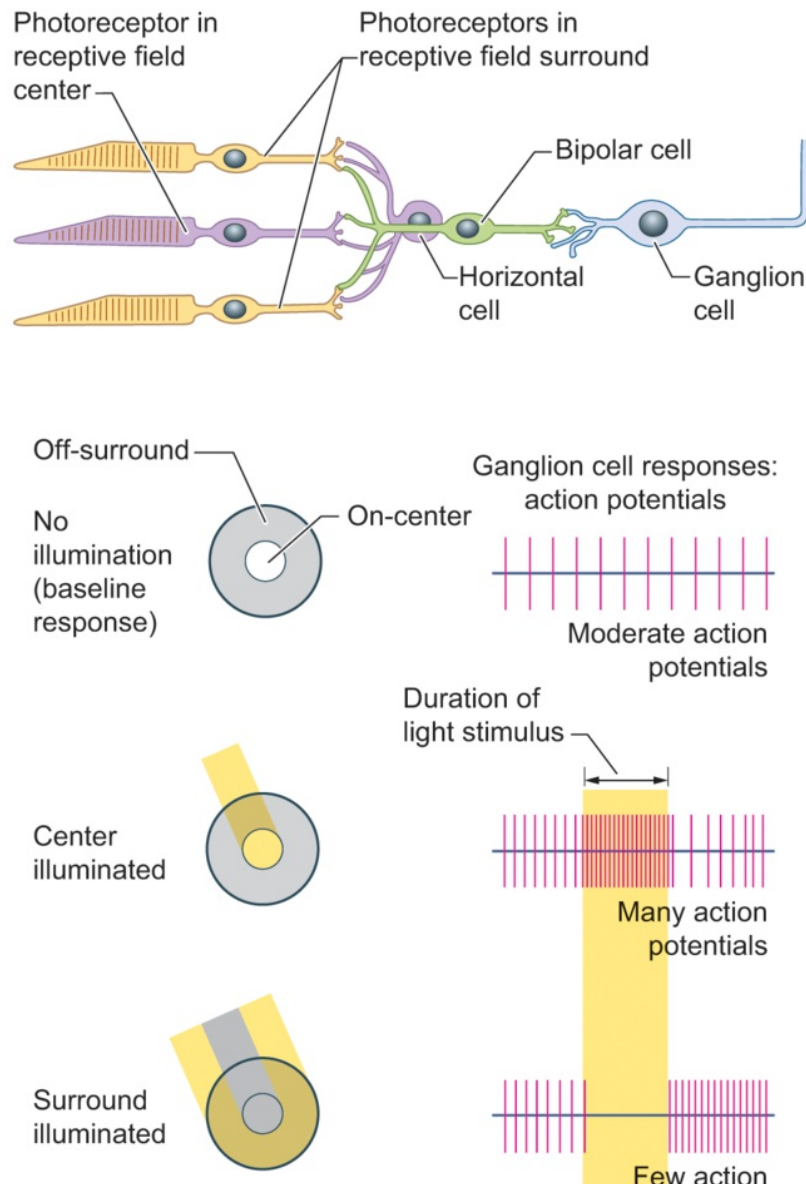
If we could record activity from one particular ganglion cell in your eye while we shone a light on different spots on your retina, most of the time we would find that this one particular ganglion cell does not get too excited. However, when the light strikes a certain portion of the retina – the precise portion that contains the rods or cones that send information to that particular ganglion cell – the ganglion cell will start firing rapidly. Keep in mind that the light has not directly struck the ganglion cell. Rather, the ganglion cell is responsive to light in that particular location of the visual world because of the rods and cones that feed into it.

If we think about the whole array of ganglion cells extending from one end of the retina to the other, we can begin to imagine how that whole array represents the pattern of light on the retina. Each individual ganglion cell only responds to light in a particular location. But different ganglion cells get input from different sets of photoreceptors in different locations, and therefore “prefer” (or respond best to) different locations; that is, different ganglion cells have different receptive fields. Thus, the pattern of activity across the array of ganglion cells represents the pattern of light across the entire retina. In other words, the brain knows where light has struck by knowing which ganglion cells are excited.

Center-Surround Receptive Fields

The receptive fields of ganglion cells are actually a bit more complex than we have just described. In particular, the receptive fields of retinal ganglion cells have what is referred to as a center-surround structure. This means that whereas light in a particular spot in visual space will excite the ganglion cell, light in the donut-shaped area

encircling that center spot will actually inhibit the cell. This type of cell has what is known as an “on-center, off-surround” receptive field. There are also cells that behave in the opposite manner. They have an “off-center, on-surround” receptive field type meaning that these cells are inhibited by light in the center of the receptive field, and excited by light in the donut-shaped surround. Although the details are beyond the scope of this chapter, the center-surround structure of ganglion cell receptive fields arises from a combination of excitatory and inhibitory inputs that the ganglion cells receive from the photoreceptors and other intermediate cells in the retina. Take a few minutes to review [Figure 5.3](#) to see the responses that different patterns of light stimuli will evoke from typical retinal ganglion cells.



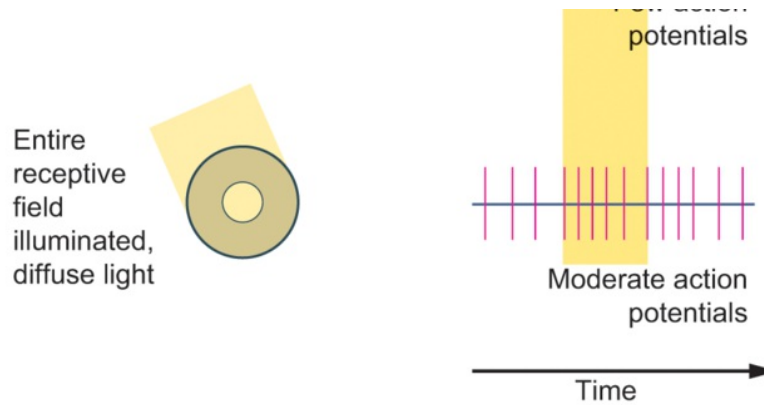


Figure 5.3 Receptive fields of ganglion cells.

Light shining on the excitatory center of the receptive field produces strong firing in the cell, whereas light in the inhibitory surround region causes the cell to slow down its firing to below its baseline rate. When light covers both the center and surround regions, the combination of excitatory and inhibitory effects results in a modest response by the cell.

You might ask: What is the point of having a [center-surround receptive field](#)? Is this just a bizarre side effect of how cells are organized, or does it accomplish some useful function? It turns out that the center-surround structure of retinal ganglion cell receptive fields can help to enhance contrast; that is, to highlight borders between light and dark areas. Because retinal ganglion cells fire best in response to spots of brightness surrounded by darkness rather than to uniform fields of brightness (or vice versa), these cells can signal the presence of contrast. This is an especially useful characteristic of retinal ganglion cells, because most objects in the visual world are defined by edges and borders. Even at the initial stages of visual processing, at the level of the retina, we have mechanisms that are specialized to signal contrast at borders. This is another illustration of how the information that the brain receives from the retina has already been partly transformed to enable our visual perception.

Pathways From the Retina to the Brain

Where does information about the visual world go once it leaves the eye? There are two main destinations for visual information that travels out of the eye along the optic nerve: the superior colliculus and the lateral geniculate nucleus (which then extends to primary visual cortex). [Figure 5.4](#) illustrates these destinations. In addition, minor projections extend to other brain regions. For example, retinal ganglion cells also send information to the suprachiasmatic nucleus of the hypothalamus, which helps to entrain bodily rhythms to daily cycles of light and dark. Here, though, we focus on the two main destinations for visual information, which demarcate the beginning of two separate anatomical paths for processing vision.

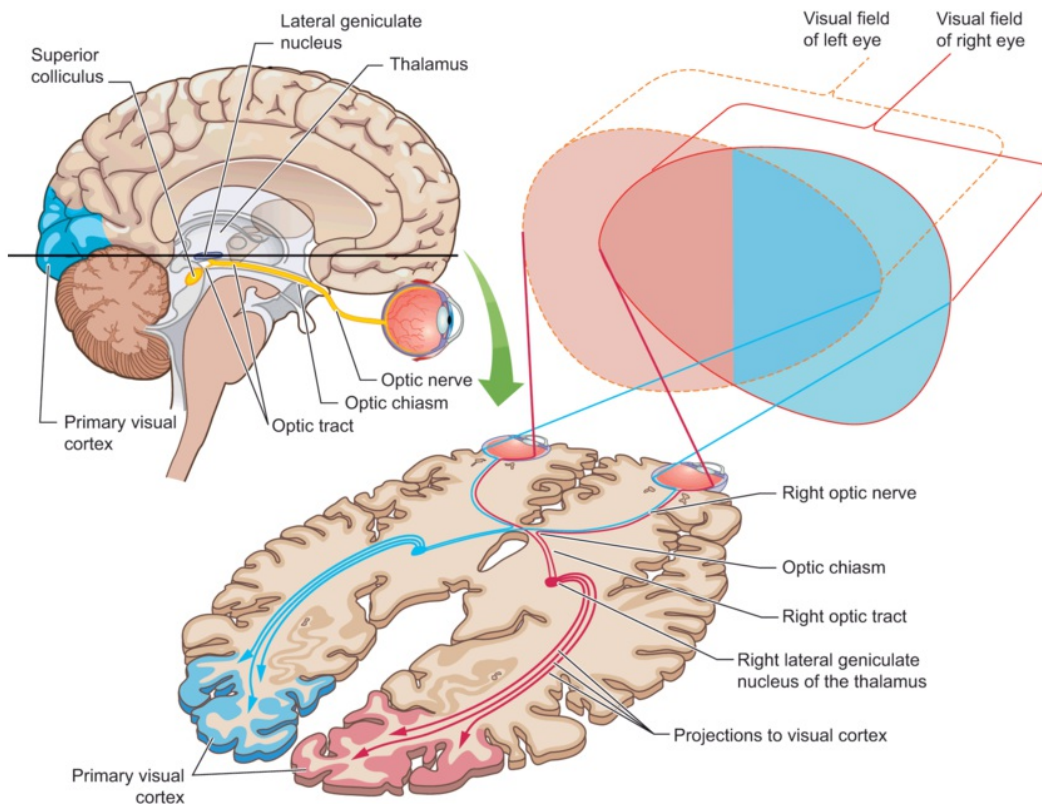


Figure 5.4 Anatomical pathways from the eye to the cortex.

Visual information leaving the eye via the optic nerve terminates in two main locations: the superior colliculus (also known as the tectum) and the lateral geniculate nucleus of the thalamus (LGN). From the LGN, visual information then travels to the primary visual cortex (also called the striate cortex). This path through the LGN and primary visual cortex is called the geniculostriate path. One feature of this path is that information from the left half of the visual world is transmitted via both eyes to the right LGN and right striate cortex, whereas information from the right half of the visual world is transmitted via both eyes to the left LGN and left striate cortex. To accomplish this, information from the nasal half of each retina (the half closest to the nose) crosses over to the LGN on the other side of the brain at the optic chiasm, whereas information from the temporal half of the retina (the half closest to the temples) travels straight back to the ipsilateral LGN.

The Tectopulvinar Pathway

The [tectopulvinar path](#) allows people to orient quickly to important visual information. For example, imagine that you are working one evening in your kitchen, and you

suddenly notice a small dark shape appear above you in your peripheral vision. You immediately turn your head and eyes toward its location, and see a bat! Before you even recognized what the shape was, your brain had already responded to it by shifting your eyes, head, and attention toward that spot. This kind of rapid visual orientation is enabled by the pathway that sends visual information from the retina directly to a midbrain region known as the superior colliculus, part of the tectum (giving the tectopulvinar path part of its name). This path is very fast-acting and is especially sensitive to motion and appearances of novel objects in the visual periphery (Krauzlis, [2014](#)). Given that the tectopulvinar path is sensitive to motion but not fine detail, you should not be surprised to learn that it receives most of its input from M ganglion cells.

Although traditionally the superior colliculus is considered to be responsive mainly to visual stimuli, it is also a site for integration of the auditory and visual senses. For example, the superior colliculus becomes active when auditory information is temporally synchronous with visual information (Dhamala et al., [2007](#)). Some individual neurons within deep layers of the superior colliculus are responsive to both auditory and visual inputs in a synergistic way, such that the neuron's response to combined audiovisual stimulation is greater than would be expected according to its response to either auditory or visual stimulation alone (e.g., Ghose et al., [2014](#); Stanford et al., [2005](#)). These multisensory properties are especially adaptive for orienting. For example, if you heard a loud "boom" at the same time as you saw a flash of light in your peripheral vision, it would be a good idea to look quickly in that direction.

From the superior colliculus, the tectopulvinar pathway extends "upstream" to the pulvinar nucleus in the thalamus and to cortical areas that process information about visual motion (Berman and Wurtz, [2011](#)). The superior colliculus also sends projections to motor regions that control eye and head movements (Krauzlis, [2014](#)). This connectivity allows a person to orient the eyes toward peripheral regions of space where important new objects or events may be occurring, so that those regions can be

brought into central vision. Once in central vision, the objects can receive more detailed analysis via the other main visual pathway, the geniculostriate pathway.

The Geniculostriate Pathway

In primates, approximately 90% of optic nerve fibers project to the [geniculostriate pathway](#), which enables our conscious experience of seeing (see [Figure 5.4](#)). Through the geniculostriate path, we are able to perceive color and all the fine-grained features that we use to recognize an infinite variety of objects and other important details in our visual world. The axons in the geniculostriate portion of the optic nerve terminate in a complex structure in the thalamus, the [lateral geniculate nucleus \(LGN\)](#). From there, the information continues to the primary visual cortex, also known as the [striate cortex](#). Therefore, the geniculostriate path gets its name because it extends to the lateral geniculate and then to the striate cortex. Because the LGN and striate cortex are each highly complex in their own right, we will deal with them individually in the next two sections.

Lateral Geniculate Nucleus

Before looking at the lateral geniculate nucleus in more detail, let's take a moment to consider how information gets to the LGN and where it lands once it arrives there. We've already discussed how retinal ganglion cells project their axons from the retina in the eye along the optic nerve, and terminate in the LGN. Information from the right sides of both retinas (which receive information from the left side of space) is sent on to the LGN on the right side of the brain, while information from the left sides of both retinas (which receive information from the right side of space) is sent on to the LGN on the left side of the brain (see [Figure 5.4](#)). For this to occur, some information must cross over from the left eye to the right side of the brain, and likewise from the right eye to the left side of the brain. The crossover point is called the [optic chiasm](#).

Once the optic nerve fibers cross at the optic chiasm, they are referred to as the optic tract, rather than the optic nerve. As a result of the crossover, the right LGN receives information only about the left half of the world (from both eyes) whereas the left LGN receives information only about the right half of the world (from both eyes). This segregation continues throughout much of the visual system; consequently, information about the two halves of the visual world is not joined together until much later, at the areas of the cortex responsible for higher levels of visual processing.

Layers of the LGN

The LGN has a beautifully layered structure (see [Figure 5.5](#)). It consists of six main layers that are stacked on top of one another, and then folded into a knee-like shape. (The word geniculate comes from the Latin root for “knee,” the same root as in “genuflect.”) Researchers have also discovered small cell layers in-between the main LGN layers. These are referred to as koniocellular or K-cell layers (Sherman and Guillery, [2014](#)). Although at present their function is not well understood, we will discuss the relevance of K-cell layers to blindsight later in this chapter.

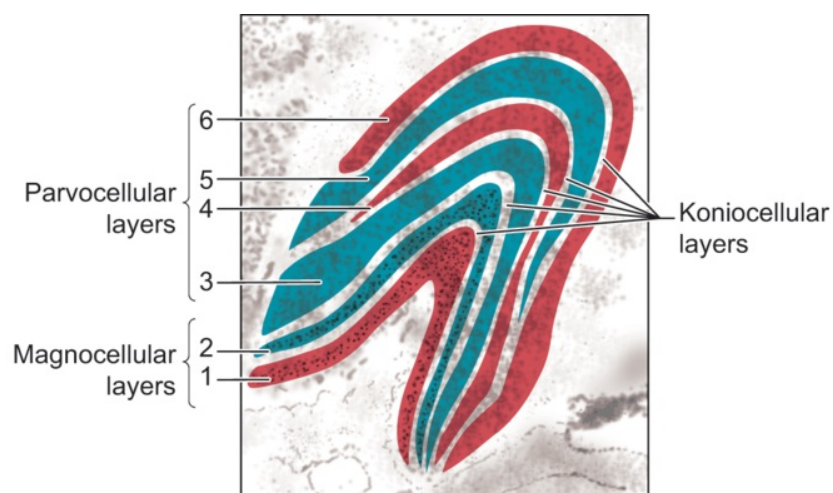


Figure 5.5 The layered structure of the LGN.

Layers 1 and 2 are the magnocellular layers, whereas 3–6 are the parvocellular layers. Input from the contralateral eye is processed in layers 2, 3, and 5, whereas input from the ipsilateral eye is processed in layers 1, 4, and 6.

How do the main layers of the LGN differ from one another? First, each layer receives input from only one eye. Some layers receive input from the contralateral eye, and some receive input from the ipsilateral eye, but all layers receive information from the contralateral visual field. So, for example, what differs between the layers in the left LGN is whether they are representing the right side of the visual world as seen by the right eye (contralateral) or as seen by the left eye (ipsilateral). Of course, the complementary pattern is evident in the right LGN.

Second, the LGN layers receive different kinds of inputs from the retina. The bottom two layers (magnocellular layers) receive input from the M retinal ganglion cells, whereas the top four layers (parvocellular layers) receive input from the P retinal ganglion cells. The koniocellular layers, which lie in between the main magnocellular and parvocellular layers, receive input from the small bistratified ganglion cells as well as from the superior colliculus.

Given what you already know about the M and P ganglion cells, you should not be surprised to learn that the magnocellular LGN layers are important for motion detection, whereas the parvocellular layers are important for perceiving color and fine detail. This functional difference was demonstrated experimentally by researchers who selectively damaged either the magnocellular or parvocellular LGN layers in monkeys (Schiller et al., [1990](#)). When the magnocellular layers were damaged, the monkeys had trouble distinguishing the direction in which a stimulus (a pattern of random dots) was moving. In contrast, when the parvocellular layers were damaged, the monkeys had difficulty distinguishing between patterns that differed only in color or in fine details (high spatial frequencies). Once again, we see how different types of processes are anatomically segregated in the structure of the visual system.

Retinotopic Mapping in the LGN

Each of the main layers in the LGN contains a retinotopic map of half of the visual world. A [retinotopic map](#) is a map that is laid out spatially like the retina itself. Neighboring cells in an LGN layer receive input from neighboring ganglion cells in the

retina, so they code for neighboring regions of the visual world, preserving the spatial organization of light patterns in the world. In other words, the spatial information coded by the retina does not get all jumbled up when it arrives at the LGN.

The retinotopic organization of the LGN was first mapped out in monkeys. To understand how cells are organized in relation to one another, the experimenter painstakingly records from one cell, then another, and then another, and tries to discern systematic relationships in terms of what stimuli excite neighboring cells. More recently, fMRI studies have confirmed that the same basic organization of the LGN holds in humans. Although fMRI does not have the exquisitely fine spatial resolution of single-cell recording, researchers using fMRI have established that each LGN receives information only from the contralateral visual field, and that information in the lower and upper fields activates superior and inferior portions of the LGN, respectively (Kastner et al., [2006](#)).

Feedback Connections to the LGN

Despite the marvelous organization of the LGN, many people have wondered what the LGN is really good for. Receptive field properties of cells in the LGN are much like receptive fields of retinal ganglion cells, so it doesn't seem that information is really transformed in any new way at this stage of the visual pathway. So, why have this stopover point on the way to the cortex?

One clue comes from the fact that most of the inputs that the LGN receives come not from the retina, but from primary visual cortex (Sherman and Guillery, [2014](#); Sillito and Jones, [2004](#)). Cortical inputs to the LGN arise from a specific layer of the visual cortex (layer 6) and they are segregated, such that different populations of cortical cells send input to either parvocellular or magnocellular layers of the LGN (Briggs and Usrey, [2014](#)).

The functional significance of these feedback connections from the cortex is still under investigation, but one possibility is that they allow the cortex to actively influence the input that it will receive from the LGN. These downward projections from the

cortex may boost the representation of some features coming from the retina or, in other cases, dampen them.

For example, imagine that you are driving down a street through the fog, looking for your friend's house. Because you've been to her house before, you know it should be on the left side of the street and that it has bright yellow shutters. This prior knowledge, presumably represented at higher levels of the visual cortex and beyond, could feed back to the LGN to enhance the firing of LGN cells that represent the location where you expect to see your friend's house, as well as enhancing the firing of LGN cells that represent patches of the color yellow. Such feedback connections could help you to find your friend's house more easily through the fog. Although this example is hypothetical, studies in both monkeys and humans have shown that the LGN's response to visual images is influenced by attention (e.g., McAlonan et al., 2008; O'Connor et al., [2002](#)).

There is still much to be learned about the functions of projections that descend from visual cortex to the LGN, but they are an important reminder that vision is not just a process of piecing together a visual image from the bottom up; that is, from retina to cortex. Rather, top-down influences – from the cortex to prior waystations in the visual stream – can shape the type of visual information that the cortex ultimately receives (see Gilbert and Li, [2013](#), for review).

Primary Visual Cortex (Striate Cortex)

Visual information finally reaches the cortex once it has passed through the LGN. The first destination within the cortex is the primary visual cortex in the occipital lobe. Specifically, projections from the parvocellular and magnocellular LGN layers enter layer IV within the six-layered cortex, and synapse with cells there. The primary visual cortex goes by many names, including V1 (because it is the first area in the cortex that receives visual information), Brodmann area 17, and striate cortex. Striate means “striped,” and refers to the appearance of this section of the cortex when viewed under a microscope (see [Figure 5.6](#)).

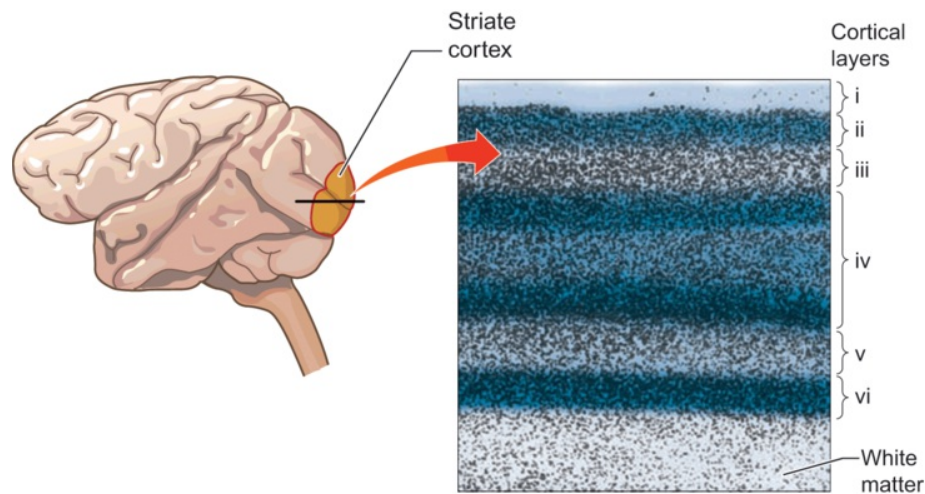


Figure 5.6 Striate cortex.

Projections from the LGN to the primary visual cortex maintain their spatial organization. That is, the left half of the visual world is represented in the right striate cortex, and vice versa. The striate cortex contains a map that is retinotopically organized, just like the LGN layers. In fact, the mapping is so precise that we can specify the [cortical magnification factor](#), which describes the millimeters of cortical surface that are devoted to one degree of angle in the visual world. (Consider that your whole visual field is about 180 degrees.) The cortical magnification value is dramatically higher for regions of the fovea compared to the periphery. In other words, much more of primary visual cortex is devoted to representing information from the center of the visual field than the periphery (see [Figure 5.7](#) for an illustration). This organization makes sense, because the fovea of the retina is packed with many photoreceptors, providing rich, fine-grained, and detailed information from the center of the visual field. In contrast, much less information from the periphery of the visual field reaches primary visual cortex.

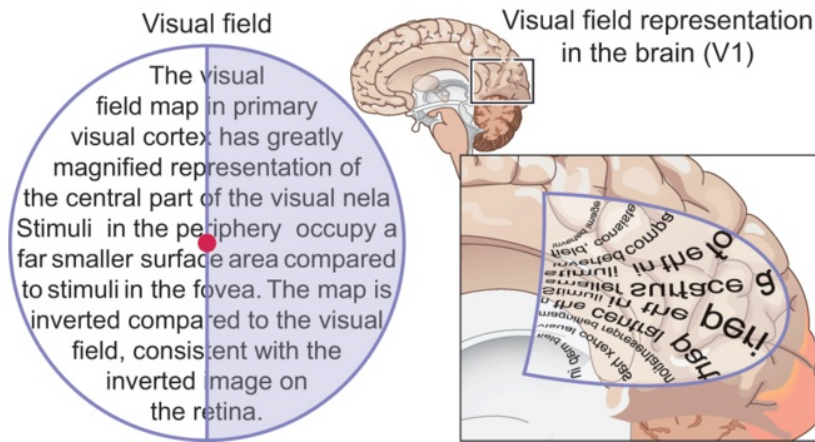


Figure 5.7 Retinotopic layout of the primary visual cortex.

If the viewer is focused on the dot at the center of the visual field, information to the left of that fixation point will be represented in the right striate cortex. The top half of the left visual field will be represented on the lower bank of the calcarine fissure (shown unfolded), whereas the bottom half will be represented on the upper bank. Note also the cortical magnification, that is, the overrepresentation of the foveal region compared to the periphery.

Organization of Striate Cortex

Visual information is represented in the striate cortex in complex ways that are somewhat different from the LGN's representation. Through pioneering work by Nobel Prize winning neurophysiologists David Hubel and Torsten Wiesel, it is known that the receptive field properties of striate cortex cells differ from those of LGN cells. (For reviews of Hubel and Wiesel's findings and the impact of their work, see Hubel, [1982](#); Kandel, [2009](#); Wurtz, [2009](#).)

There are several types of striate cortex cells, referred to as simple, complex, and hyper-complex (or end-stopped) cells. What they all have in common is that their receptive fields are no longer tuned to spots of light, as LGN cells are. Instead, they are responsive to bars of light oriented in particular ways. A simple cell's receptive field is bar-shaped, with an excitatory center and inhibitory surround, but the cell will only fire if the bar is oriented in a particular way (see [Figure 5.8A](#)). Different [simple cells](#) respond to bars of different orientations. [Complex cells](#) are like simple cells in that they

respond best to certain line orientations, but complex cells are less picky about where exactly the line is located, they do not have on and off regions, and they show a preference for lines that are moving in a particular direction, such as from left to right (see [Figure 5.8B](#)). **Hyper-complex**, or end-stopped cells, prefer lines of certain lengths; as a line gets longer, at a certain point a hyper-complex cell will become less excited by it.

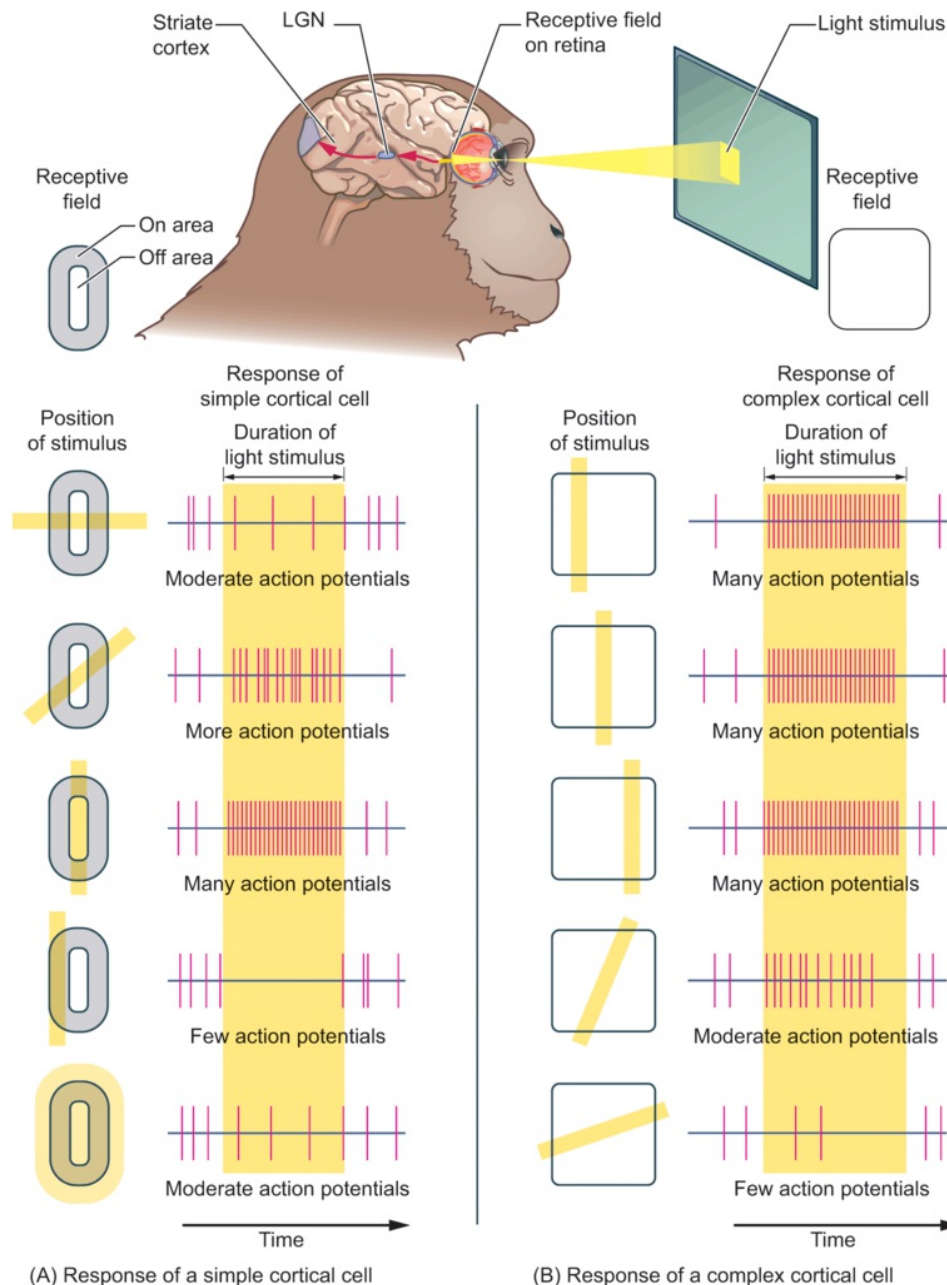


Figure 5.8 Receptive fields of simple and complex cells.

Simple-cell receptive fields (panel A) are constructed such that the cell responds best to a bar of light oriented in a particular direction and surrounded by darkness. Complex cells (panel B) are less selective about the placement of the line, but still prefer a certain orientation.

As illustrated in [Figure 5.9](#), within the chunk of cortex representing each spatial location, there is a systematic organization of cells that respond to all the various line orientations. Cells that prefer a given line orientation are grouped together, forming

orientation columns. Neighboring columns contain cells with similar orientation preferences. For example, cells in one column might respond best to lines oriented at 40 degrees while cells in a neighboring column might respond best to lines oriented at 42 degrees. Thus, across a chunk of cortex, all the various orientations are represented. Orientation columns also contain cells that are tuned to respond best to certain directions of motion. Orientation columns also contain cells that are tuned to respond best to certain directions of motion.

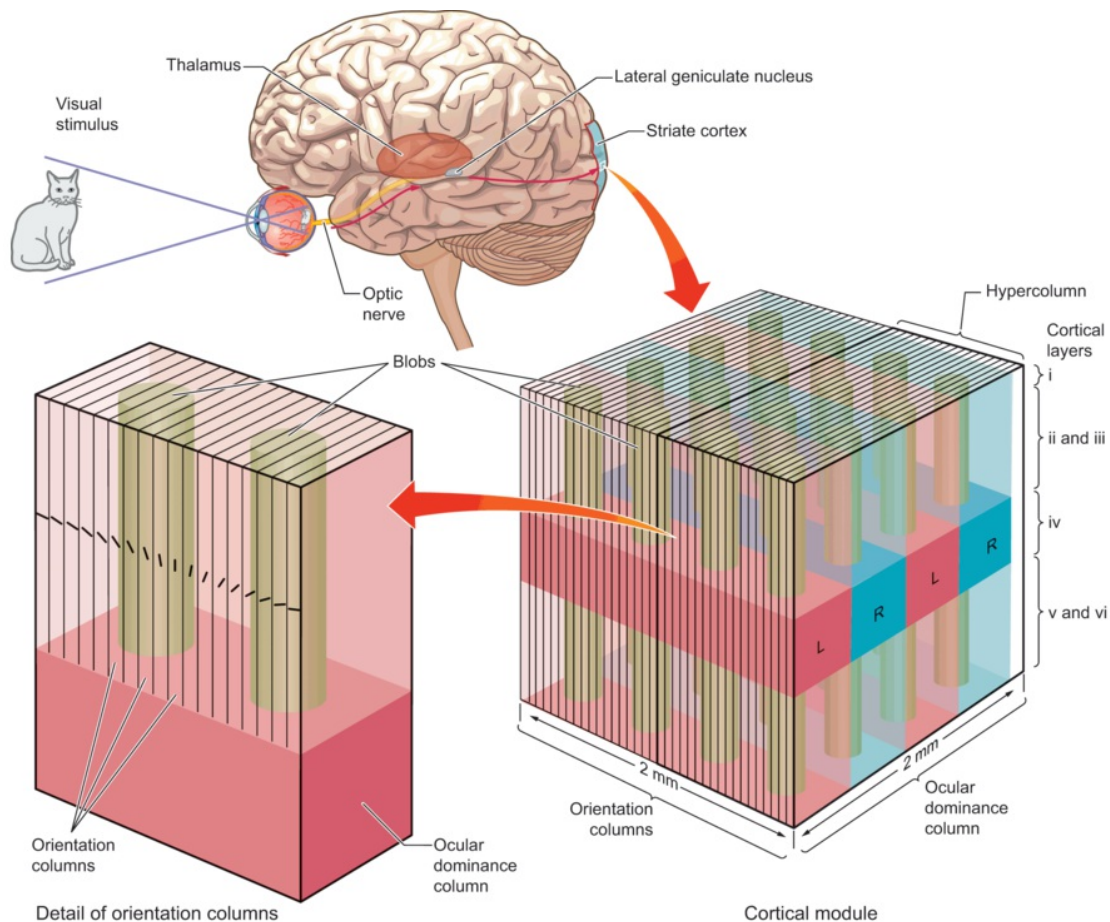


Figure 5.9 Hypercolumns in striate cortex.

A 2 mm x 2 mm chunk of cortex contains subcolumns corresponding to ocular dominance and orientation columns. Each subcolumn contains cells that are especially responsive to lines of particular orientation as seen by either the left or the right eye.

In addition, cells are segregated into columns according to which eye sends them input. These columns are referred to as ocular dominance columns. For example, within

layer IV of the striate cortex, cells in one column respond only to input from the left eye, whereas cells from another column respond only to input from the right eye.

Putting all of this together, we have an exquisite organization in which a hypercolumn contains cells that are all tuned to respond to stimulation at a particular spatial location. Within that hypercolumn, there are subcolumns of cells that prefer particular orientations and that receive inputs from particular eyes. Furthermore, running vertically through these hypercolumns are also areas cleverly known as “blobs,” which contain cells that are especially involved in coding color information.

The entire retinotopic map is made up of a series of these hypercolumns, each corresponding to a different retinal location (see Ts'o et al., [2009](#) for a review). Across a whole array of hypercolumns, all orientations at all points in space are represented. (At least for the half of space that that side of striate cortex is responsible for representing, i.e., the left half of space for the right striate cortex, and vice versa.) This hypercolumn model of organization across the cortical surface is sometimes informally referred to as the “ice cube tray” model, based on typical textbook depictions such as the one in [Figure 5.9](#).

Given this beautifully organized map, it is tempting to think that a little person inside your brain could look down on the striate cortex and figure out the pattern in the visual world by noticing which cells are firing, indicating the presence of oriented lines and edges at certain spatial locations. In theory, someone who was given all the information represented in striate cortex could deduce much about the actual scene out in the world. However, there is no little person inside your brain who watches the striate cortex. There are only other brain regions. As we will see in later chapters, other brain regions use the information provided by the striate cortex in the service of certain goals, such as object recognition and spatial navigation.

Binocular Integration in Striate Cortex

One important aspect of the organization of primary visual cortex is that information from the two eyes is integrated, unlike the LGN in which inputs from the two eyes are kept segregated in separate layers. At the level of the LGN, there is no way for visual information from the two eyes to be directly compared. Why is it ultimately important to compare information from the two eyes? Another way of asking this question is to ask why we even have two eyes in the first place.

The main reason for having two eyes is to enable depth perception. To reach for a cup, you need to know how far away it is so that you know how far to stick out your arm. However, the retina only records the spatial location of light patterns in two dimensions. Depth must be computed by the brain, because it is not directly coded by the retina.

One of the most important cues for depth computation is binocular disparity. **Binocular disparity** refers to the fact that the image that falls on each retina is slightly different, because the eyes are positioned in different locations. Importantly, the images on the two retinas are more discrepant when items are close to the viewer and less discrepant when they are further away. The brain uses this information to determine an item's depth in the visual world.

Some cells in striate cortex are especially tuned to certain amounts of binocular disparity (for review, see Freeman, [2014](#)). The cells in layer IV of the striate cortex, which receives the primary projection from the LGN, are monocular, meaning that they respond only to information from one eye (as described in the discussion of ocular dominance columns above). However, cells in striate layer IV then connect with cells in other striate layers in ways that allow for the convergence of information from both right-eye and left-eye ocular dominance columns.

The binocular cells created through such convergence are sensitive to particular amounts of disparity, or discrepancy of inputs from the two eyes. Because different binocular cells code for (are most sensitive to) different amounts of binocular disparity, a population of such cells can represent all possible depths of an oriented line. Higher-level cortical brain regions can then make further use of this binocular disparity

information, such as using depth information as a cue to an object's three-dimensional shape or its location (Parker, [2014](#)). For example, when a stick-like object appears close to the viewer, it is more likely to be perceived as a matchstick, while a similar object positioned in the distance is likely to be perceived as a tree.

Contextual Modulation of Cells in Striate Cortex

Another characteristic of cells in striate cortex is that their responsiveness can be modified by context (Lamme, [2004](#); see also Flevakis and Murray, [2015](#)). Although information outside a cell's receptive field cannot alone cause the cell to fire, such information can modulate the cell's response when presented together with the cell's favored stimulus.

To illustrate this idea, consider a cell that fires maximally to the location and orientation of the line in the center of [Figure 5.10A](#). When this line falls within the cell's receptive field, the cell responds by increasing its firing; nevertheless, the magnitude of that response to the line can be modulated by the surrounding context. For example, studies have found that in the monkey striate cortex, a cell whose classical receptive field corresponds to the line in part A of [Figure 5.10](#) will fire less strongly when the surrounding lines all go the same way, as in part B. This corresponds to our perception: the line segment seems more salient in panel A, when it appears against a blank background, compared to panel B, when it appears as part of a group. Likewise, the cell's response to the array in part C is stronger than its response to panel B, again aligning with our perception that the line "pops out" more in C than in B.

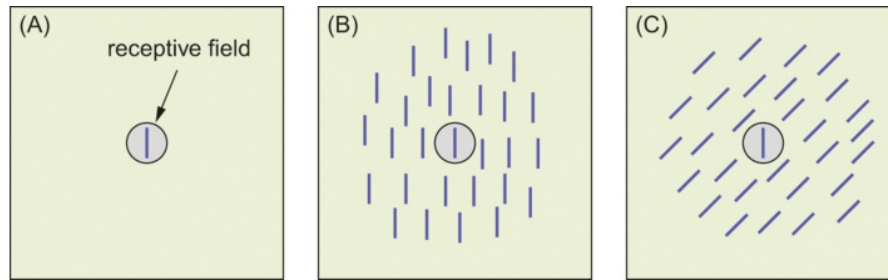


Figure 5.10 Perception of a line segment depends on its context.

In panel A, the line in isolation is easy to distinguish from its background, whereas in panel B, it is less distinguishable from the other lines. In panel C, the middle line segment “pops” out of the array. Single-cell recordings in monkeys show that the surrounding elements influence the activity of a cell whose receptive field corresponds to the center line segment.

Contextual modulation and its influence on striate cortex cells may even help to explain what perceptual psychologists refer to as figure–ground segregation (Lamme, 2004). In [Figure 5.11A](#), you probably perceive a square, or figure, against a background. The orientation of the lines within the square differs from the orientation of the lines outside the square, creating the sense of a square shape against a background. Now, imagine a striate cortex cell whose receptive field corresponds to the small circle indicated in the center; that is, the cell responds best to lines of that orientation in that location. Will this cell’s response differ depending on whether the whole array looks like A or B? The answer is yes. When the preferred stimulus – lines oriented a particular way – appears to be part of a figure, the cell responds more strongly than when the preferred stimulus appears to be part of a background. Keep in mind that the stimulation provided by information in the receptive field itself is exactly the same in these two cases; the only thing that differs is the surrounding context.

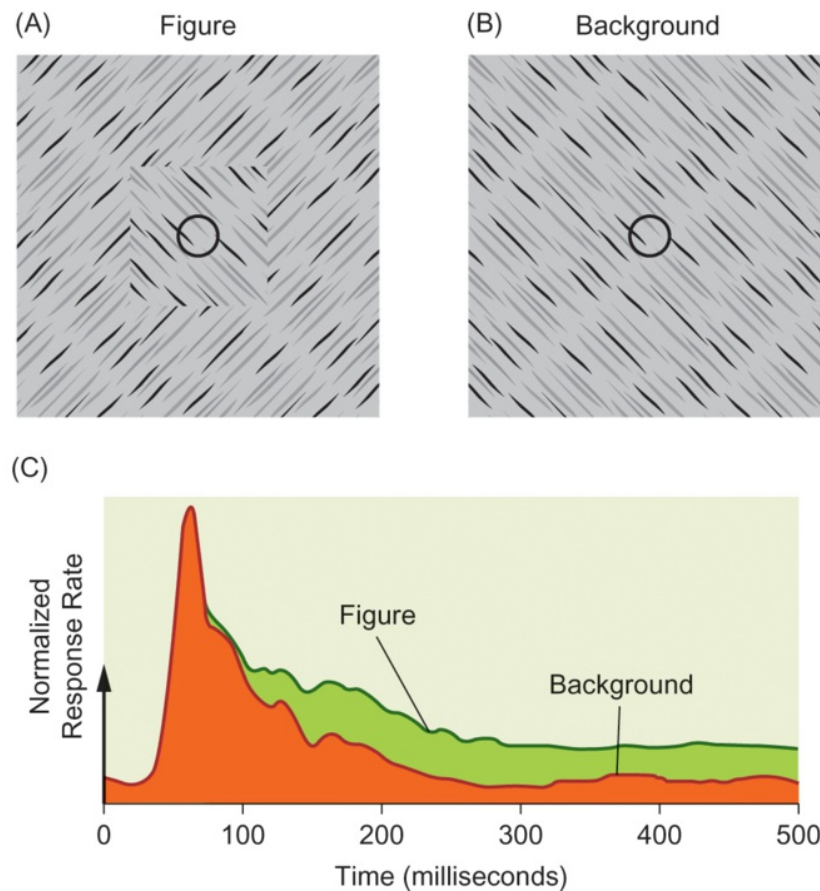


Figure 5.11 Perception of figure and ground.

In the example in the left, in (A), you perceive a square against a background, whereas the example on the right, in (B), appears to be all background. As illustrated in (C), cells whose receptive fields are tuned to the center of this array will fire more strongly when the oriented lines in their receptive fields are perceived to be part of a figure, compared to when those same lines appear to be part of a background.

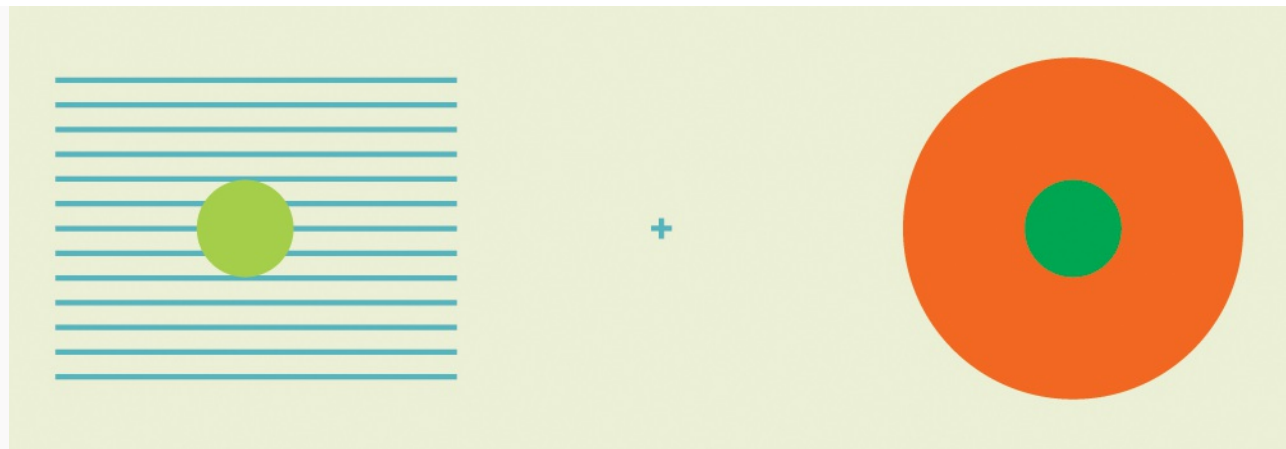
These contextual effects tell us that the activity of cells within the striate cortex is not just driven by inputs that individual cells receive from the retina and LGN (Gilbert and Li, [2013](#)). Rather, the striate cells' activity is also driven by additional information about the local context. This additional information could be coming from two sources: neighboring cells within the striate cortex that send lateral connections to one another, or feedback projections from higher levels of the visual system. Evidence indicates that both of these sources can influence the activity of striate cells.

Once again, while there is an appealing simplicity to a bottom-up model (also called a feed-forward model), in which information is pieced together step-by-step through ascending stages of the visual system, a more realistic view of the visual system incorporates not only a feed-forward route of information flow, but also feedback connections that can modulate processing at earlier steps in the ascending hierarchy. In this way, the salience of certain types of visual information can be modulated depending on the context.

In Focus: Seeing What's Not There: Visual Illusions and the Striate Cortex

Do you ever see things that aren't really there? Well, yes. Some researchers refer to such perception as “nonretinal vision” or “phantom perception,” which can range from simple perceptual illusions to more complex kinds of mental imagery and hallucinations (Pearson and Westbrook, [2015](#)). The most benign example is a phenomenon known as perceptual filling-in of the blind spot. Studies of the role of striate cortex in this phenomenon provide fascinating clues about how the brain can create a perception of visual features even when those features are not actually registered on the retina.

As you may know, each of your two eyes has a blind spot, created by an area in the retina where there are no photoreceptors. The [blind spot](#) is the point at which all the ganglion cell fibers are gathered together in a bundle to exit the eye as the optic nerve (look back on [Figure 5.1](#)). In daily life, you do not even notice your blind spot. Why not? It could be because you have two eyes, and the blind spot is placed in a slightly different location in each eye. However, if you close one eye, you still do not notice the other eye's blind spot at all: there is no noticeable “hole” in your perception of the visual world. Your visual system perceptually fills in this missing information as if the background just continued on through the blind spot. You can experience this phenomenon for yourself using the image in [Box Figure 5.1](#).



Box Figure 5.1 Illustration of filling-in of the blind spot.

Try closing your right eye and fixating your gaze on the small cross in the middle of the figure. Now, move the page closer to your face. At some point (about 15 cm), you should notice that the green circle in the center disappears, and the rectangle appears uniformly striped. You can also try to find the blind spot in your right eye by closing the left eye and repeating the procedure using the circle on the right side of the figure. At some point, the green circle in the middle should disappear.

Recent evidence indicates that this filling-in process is carried out, at least in part, in primary visual cortex (Komatsu, [2006](#)). Clever studies have recorded signals from individual cells in the monkey striate cortex in regions of the retinotopic map that correspond to the blind spot (Azzi et al., [2015](#); Matsumoto and Komatsu, [2005](#)). When the monkey views a stimulus that falls in part across the monkey's blind spot, such as a line with a particular orientation, the striate cortex cells coding for that stimulus still fire. In other words, even though this stimulus is not represented at the level of the retina (because it falls on the blind spot), the primary visual cortex still codes for that feature as if it were there. Results from human brain imaging also find that striate cortex is activated by features that fall within the blind spot (Tong and Engel, [2001](#); see also Meng et al., [2005](#)).

How can this happen, if those features are not actually registered on the retina? Although the actual mechanism is still unknown, one possibility is that the cells representing that particular feature are stimulated by spreading activation from excited cells nearby, leading to a kind of interpolation of the missing feature (Spillmann et al., [2006](#)). Another possibility is that cells representing the blind spot have large receptive fields that extend beyond the blind spot, and thus their activity is influenced by stimulation right around the blind spot (Komatsu, [2006](#)).

It is useful to have the blind spot filled in, because it would be distracting to walk around with two little holes in your view of the world. However, the phenomenon of filling-in can also make it harder to notice certain kinds of brain damage. For example, imagine someone who sustains a small lesion to a part of the retinotopic map in the LGN or striate cortex. Such a person would have a [scotoma](#) (a blind spot) in a certain part of the visual field. Often such people do not even notice these acquired blind spots because the brain “fills them in.” Such a scotoma may be discovered only through systematic testing of the visual field by an ophthalmologist.

Other illusory phenomena also illustrate that conscious perception is not driven solely by the bottom-up input from the retina. One example comes from the study of [binocular rivalry](#). Imagine that you looked into a special machine that showed a picture of a rose to your right eye and a picture of a lemon to your left eye. First, note that this kind of situation would never happen in the natural world; you would never normally see a rose and a lemon occupying the same space in the world. Your visual system is not really set up to handle this situation, because it evolved to cope with situations that actually exist in the natural world. Still, your visual system does not crash completely when presented with this bizarre scenario. Rather, it does something interesting: It creates a perception that oscillates back and forth between seeing the lemon and seeing the rose.

Vision scientists have used binocular rivalry as a special trick to test how neural firing in different brain regions coincides with conscious perception. Here we have a scenario where the visual input remains the same – rose and lemon together – but the conscious perception oscillates – rose, lemon, rose, lemon. Research using binocular stimuli has shown that activity in striate cortex is correlated with the pattern the person is consciously perceiving at that moment (Polonsky et al., [2000](#)). This suggests that the striate cortex is not just coding for what appears on the retina (because in the case of binocular rivalry, the retinal image remains unchanged); rather, it is coding for the features that are consciously perceived.

Controversy still exists about whether changes in striate cortex activation actually cause the shift in conscious perception between the rival stimuli, or whether the striate cortex is responding to higher-level brain regions that drive the change in conscious perception (see Blake et al., 2014). Interestingly, recent research using optical imaging found that binocular rivalry effects occur in striate cortex even in monkeys who are anesthetized and therefore not consciously aware (Xu et al., [2016](#)). Specifically, the study found that in a binocular rivalry situation, activity oscillated between left-eye and right-eye ocular dominance columns in striate cortex in an anesthetized monkey in much the same way as when an awake, conscious monkey viewed the same stimulus. This evidence implies that conscious awareness is not the cause of rivalry effects in striate cortex, because rivalry effects can occur in the striate cortex without consciousness. Instead, it may be that the rivalry effects in striate cortex provide information that gives rise to conscious perception mediated by some later step in the perceptual processing pathway. Regardless, these studies make clear that the brain actively constructs a representation of the visual world, even as they leave open intriguing questions about how conscious perception arises.

Visual Areas Beyond the Striate Cortex

The striate cortex is the first cortical processing center for vision, but it is by no means the last. Dozens of additional cortical regions have been implicated in aspects of vision. Striate cortex provides a representation of numerous features of the visual world, but that information must be further processed and transformed before it can be fully useful in understanding and acting upon the world.

Multiple Maps of the Visual World

One fascinating finding by vision scientists is that there are many maps of the visual world within the brain. We have focused in detail on the retinotopic maps in the LGN and primary visual cortex, but similar maps also exist in regions beyond the striate cortex – that is, in so-called “extrastriate” regions of visual cortex.

[Figure 5.12](#) illustrates the location of several of these additional regions, named V2, V3, and V4, in the macaque monkey brain. Each of these areas is retinotopically mapped, like primary visual cortex (V1). For example, area V2 in the right hemisphere contains a map of the left visual field, as does area V3. Generally speaking, the dorsal half of each of these regions represents the lower visual field and the ventral half represents the upper half of the visual field.

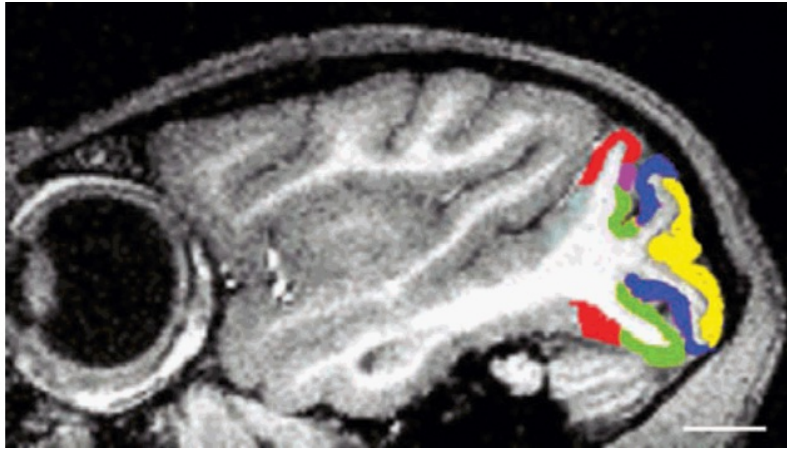


Figure 5.12 Location of striate and extrastriate visual areas in the macaque monkey cortex.

Note that areas V2, V3, and V4 are split into dorsal and ventral halves.

Source: Wandell, B. A., and Wade, A. R. (2003). Functional imaging of the visual pathways. *Neurologic Clinics of North America*, 21, 417–443. Reprinted by permission of Elsevier.

Like retinotopic maps elsewhere in the brain, the maps in V2, V3, and V4 have been investigated using single-cell recording in monkeys, in which the receptive fields of individual cells are located and compared with those of neighboring cells. More recently, researchers have used fMRI to study retinotopic mapping in the human cortex. To identify retinotopic maps with fMRI, researchers systematically present stimuli that differ in their eccentricity (degree of distance from the fovea) as well as stimuli that differ in their polar angle (location from the center on a wedge shape). The kinds of stimuli typically used in these experiments are shown in [Figure 5.13](#). Researchers present many combinations of these kinds of stimuli in an attempt to determine the part of the visual field to which a certain region of the cortex is most responsive (Wandell and Wade, 2003; Wandell and Winawer, 2015).

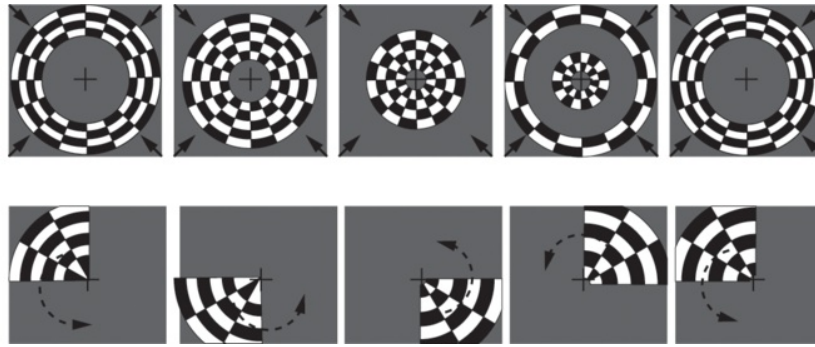


Figure 5.13 Types of stimuli used to map out retinotopic coordinates in cortical regions in humans.

On the top are stimuli that differ in eccentricity. Notice that the stimulus in the middle will mainly stimulate foveal areas, whereas those on the two ends are likely to stimulate peripheral areas. Comparing the brain regions activated by these two types of stimuli provides information on which portion of brain tissue represents the fovea and which represents the periphery. On the bottom are stimuli that differ in polar angle. These stimuli are used to determine which quadrants of the visual world are mapped onto which portion of visual cortex.

One obvious question has probably occurred to you. What is the point of having all of these retinotopic maps? (And there are known to be many more than these three!) Does each area – V1, V2, V3, and V4 – serve a different function? Do they represent different properties of the visual world?

The answer is that we simply do not know the functions of all the visual maps beyond V1, although they seem to represent properties of a visual image that are more complex than that encoded by cells in V1. For example, cells in area V2 appear to differentiate between naturalistic textures. Imagine, for example, the differences in visual characteristics that provide information about the texture of grains of rice compared to fibers in a wool rug or bricks in a wall (Freeman et al., [2013](#)). Another extrastriate area known as area MT (also called V5) has been linked to motion perception, as we will discuss in much more detail in [Chapter 7](#). Area V4 has been posited to play a special role in color perception, although that claim has been controversial. In the [next section](#), we focus on the role of V4 in color perception to

illustrate the challenges posed by attempting to associate a particular extrastriate region with a particular perceptual function.

Area V4: A Special Module for Coding Color?

Observations of brain-damaged patients originally gave rise to the idea that a subregion of visual cortex may be especially responsible for color vision. Patients with [cerebral achromatopsia](#) have damage to the visual cortex that results in a perceptual experience that is devoid of color (for review, see Bouvier and Engel, [2006](#)). Such patients report that the world appears in shades of gray, and they often have trouble naming colors or differentiating stimuli on the basis of color alone. Because these patients typically have damage to the posterior ventral cortex, it is logical to infer that some subregion within this area plays an important role in color perception.

At the same time, it is important to note that there do not appear to be any cases of “pure” achromatopsia, in which every other aspect of vision is perfectly normal except color perception. Instead, individuals with achromatopsia tend to also have problems with aspects of spatial vision and pattern recognition (Bouvier and Engel, [2006](#)). The absence of a pure case of achromatopsia could be because brain damage is seldom precise, rarely affecting just a small circumscribed region of cortex. Therefore, damage is likely to affect nearby visual regions as well as a presumably small “color area.” Alternatively, the absence of a pure case may suggest that there is no “color area” that processes color information exclusively. We must look to methods besides the lesion method to further address this question.

More than 30 years ago, researchers identified cells within the V4 area of the macaque monkey that appeared to be especially sensitive to color (Zeki, [1973](#)). Even more exciting, these cells seemed to demonstrate color constancy (Zeki, [1983](#); see also Kusunoki et al., [2006](#)). [Color constancy](#) refers to a perceptual phenomenon in which a color appears similar across many different lighting conditions. For example, your favorite red sweater looks “red” whether you see it lit by a dim incandescent bulb or by

a bright fluorescent bulb, despite the fact that the source of illumination differs quite dramatically and therefore the wavelengths reflected back by the sweater also differ dramatically. Because your perception of the sweater as “red” persists across these different conditions, your brain must be computing color by taking into account the wavelengths and intensity of the background illumination. The discovery that cells in the V4 area exhibit color constancy – preferring a particular color regardless of the illumination – suggested that this region might be crucial for the computations necessary for color constancy.

Yet, other studies found that V4 cells in the monkey are responsive to properties other than color, such as line orientation, depth, and motion (e.g., David et al., [2006](#); Hegdé and van Essen, [2005](#); Li et al., [2013](#)). Subsequent studies that combined fMRI and single-cell recording in monkeys found that V4 is composed of clusters of cells that are color-sensitive interspersed with clusters of cells that are not color-sensitive (Conway et al., [2007](#); see also Li et al., [2014](#); Tanigawa et al., [2010](#)). These studies indicate that V4 is not composed of a single set of cells with a uniform function. They also remind us of the limitations of single-cell recording, in which only a small number of the millions of cells in a given region are sampled.

To examine color processing in humans, neuroimaging studies have typically compared conditions that involve making color discriminations to conditions that involve making brightness discriminations among grayscale stimuli (e.g., Bartels and Zeki, [2000](#); Hadjikhani et al., [1998](#); Lafer-Sousa et al., [2016](#)). Such studies have reported that the color condition activates areas on the ventral surface of the occipital lobe, corresponding fairly well with the location of lesions in patients with achromatopsia (see [Figure 5.14](#)). However, controversy persists about what these areas should be called, specifically whether they are truly homologous to the monkey V4 area in the sense of sharing a common evolutionary origin and function (see Wandell and Wade, [2003](#) for a review).

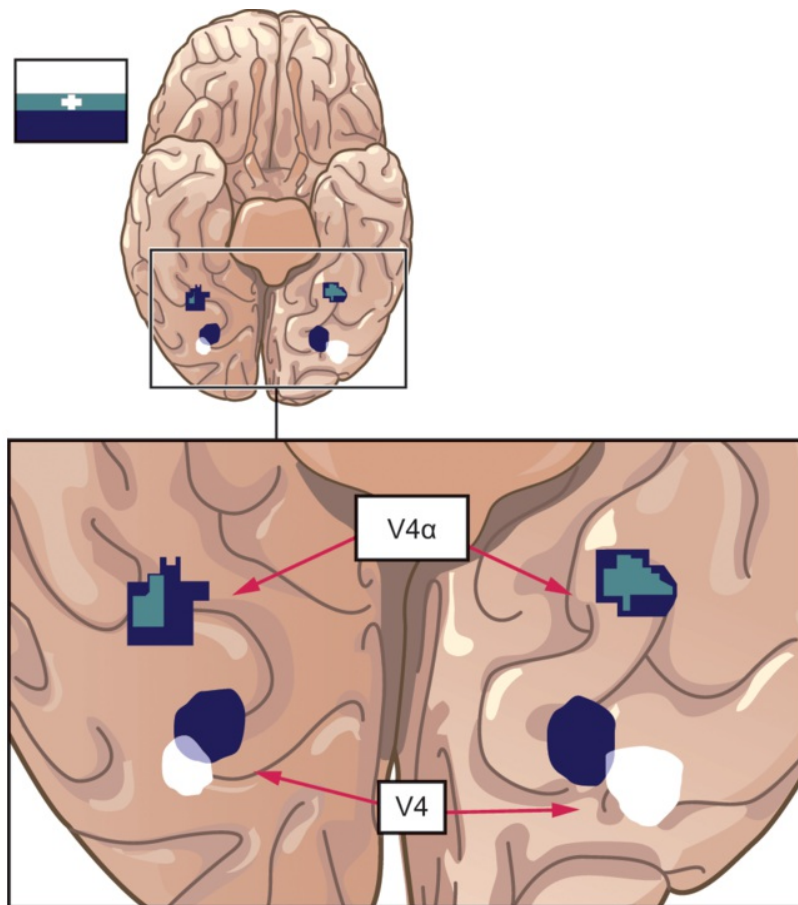


Figure 5.14 Color-sensitive regions of the ventral visual cortex.

This study by Bartels and Zeki ([2000](#)) found two regions that were sensitive to color information. A more posterior region, called V4, has a retinotopic organization, as seen by the finding that stimulation of the upper and lower visual fields leads to responses in slightly different subareas of this region. The more anterior color-sensitive region (labeled V4 α) does not appear to be retinotopically mapped, because stimulation of upper and lower visual fields leads to overlapping activation.

So, what conclusion should we reach regarding area V4 and color perception? Clearly, the idea that V4 is the brain's "color center" is far too simplistic (Roe et al., [2012](#)). Human neuroimaging and patient studies imply an association between ventral extrastriate subregions and color processing, but the exact nature of the association – how to define different subregions, and what unique contribution each one makes to color perception – is still subject to debate. Cells in V4 of the monkey seem to code for color but also other perceptual attributes such as form and motion. Furthermore, cells in

earlier areas of the visual stream (such as V2 and V3) also appear to code for color information (as do regions more anterior to V4; Gegenfurtner and Kiper, [2004](#)).

Therefore, V4 does not appear to be unique in its color sensitivity. Rather, color is an attribute that is coded at several levels of the visual processing stream, beginning with the cones in the retina and extending through parvocellular layers of the LGN, the striate cortex, and extrastriate areas V2 and V3, as well as V4 and more anterior regions. Although in this section we have focused in depth on area V4, the lessons of this discussion extend to other visual cortical regions as well. As researchers face the challenges of associating structure with function in visual perception, simplistic models, in which each identifiable anatomical region is a self-contained module responsible for a particular aspect of perception, are unlikely to hold up over time.

Blindsight and the Visual Pathways

At this point in our review of visual pathways, it can be useful to think back on the case study of blindsight at the beginning of this chapter in which such people have no conscious experience of “seeing,” because of extensive damage to the striate cortex, yet are able to make rudimentary visual discriminations. Understanding what pathways are responsible for the patients’ intact visual abilities can help us to appreciate a bit more the functions served by different visual pathways in the brain.

People who have sustained damage to the primary visual cortex typically experience [cortical blindness](#), which means blindness of cortical origin rather than due to a problem in the eye or optic nerve. If the damage affects the primary visual cortex in both hemispheres, this cortical blindness will extend across the whole visual field. If only one hemisphere is damaged, the patient will be hemianopic for the opposite (i.e., contralateral) visual field. These patients report being blind for all information in the affected visual field, with no sense of either dark or light.

Among patients with cortical blindness, only a very small proportion display blindsight, in which special testing reveals that some aspects of vision appear to be

preserved, even though the patient's subjective experience is of being blind. In the most basic sense, cortical blindness tells us that the primary visual cortex is necessary for conscious awareness of the visual world. But blindsight tells us that an intact primary visual cortex is not necessary for all aspects of vision, because some aspects of vision appear to be preserved even when the primary visual cortex is damaged.

Although there is some variability in the preservation of visual functions across different patients with blindsight, a review of the extensive testing done on these patients suggests several common areas of preserved function (Weiskrantz, [2004](#)). Patients with blindsight can localize spots or bars of light by pointing or moving their eyes toward the targets; they can distinguish the orientations of lines that differ by about 10 degrees; they can distinguish when a target is moving or stationary; and they can make some basic color judgments, such as determining whether a square is red or gray. Patients may also show some knowledge of visual form; for example, a patient might adjust the hand appropriately for grasping a particular object in the blind field. In all of these areas, performance is above what would be predicted by chance, but still far below what normal vision would support. Furthermore, the patients report that they are completely guessing and have no perceptual experience of "seeing" in the blind field.

Researchers disagree about what part of the visual system carries out the preserved functions in people with blindsight. One possibility is that blindsight is supported by an intact tectopulvinar system paired with a damaged geniculostriate path. This explanation has intuitive appeal because it fits with the idea that the tectopulvinar system carries out more rudimentary visual processing, which can support orienting to basic visual information while not allowing higher-order visual awareness.

Some evidence for this viewpoint comes from a study that demonstrated the integrity of the tectopulvinar system in individuals with blindsight (Leh, Johansen-Berg, and Ptito, [2006](#)). Using diffusion tensor imaging, researchers examined projections arising from the superior colliculus (part of the tectopulvinar path) in three groups: patients with blindsight in the contralateral visual field following hemispherectomy, patients with hemispherectomy but with no residual visual abilities in the contralateral visual

field, and control patients with no brain damage. In patients with blindsight abilities but not those without, the superior colliculus in the damaged hemisphere was connected by fiber pathways to a variety of cortical regions in the opposite hemisphere, such as primary visual cortex and visual association areas (see [Figure 5.15](#)). In fact, these connections seemed to be even more pronounced than in non-brain-damaged control subjects. Additionally, when input to the tectopulvinar system is blocked, some patients with blindsight lose their residual vision. For example, researchers cleverly took advantage of the fact that the superior colliculus does not receive any information from short-wavelength-sensitive cones (i.e., those sensitive to blue light) (Leh, Mullen, and Ptito, [2006](#); see also Tamietto et al., [2010](#)). When blindsight patients were asked to distinguish stimuli of these wavelengths, their limited “sight” disappeared! These results fit with the idea that residual function in blindsight depends on the tectopulvinar system.

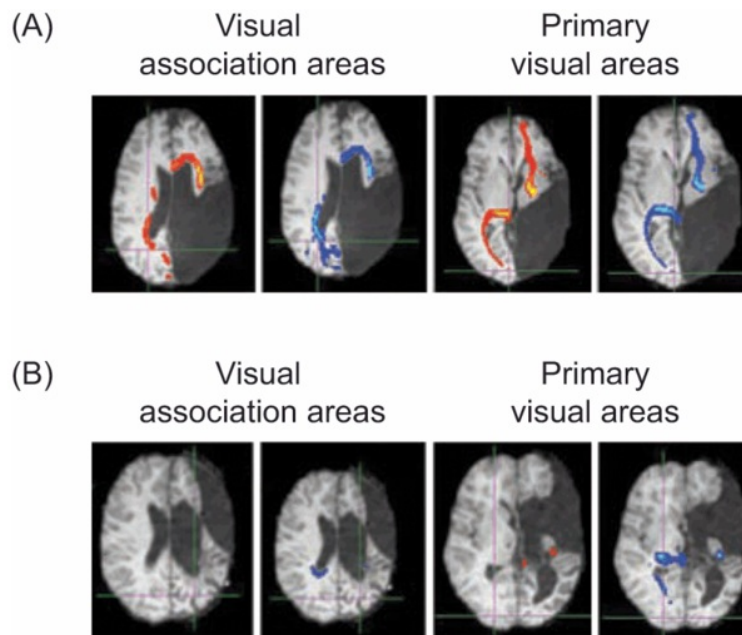


Figure 5.15 Intact projections from the superior colliculus in blindsight.

Panel (A) shows intact anatomical pathways connected to the right superior colliculus (in red) and the left superior colliculus (in blue) for a patient with blindsight (residual vision) after hemispherectomy. Panel (B) shows the absence of such pathways in a patient with a hemispherectomy but no blindsight capabilities. In both patients, the dark gray area represents the missing tissue due to the hemispherectomy.

Another route that may mediate the intact visual capabilities in blindsight involves pathways from the LGN to cortical visual areas that bypass primary visual cortex. Although the major projection from the LGN goes to the primary visual cortex, the LGN also sends minor projections to other cortical visual areas. In monkeys, the koniocellular or K-cell layers of the LGN project directly to extrastriate cortical areas that are especially sensitive to information about motion, such as area MT/V5 (Sincich et al., [2004](#)). A neuroimaging study of one patient with pronounced bilateral damage to striate cortex found that area MT was activated in response to visual stimuli even though the striate cortex was not (Bridge et al., [2010](#)). Furthermore, a diffusion tensor imaging study found that among patients with damage to striate cortex, the patients with preserved blindsight abilities had intact white-matter pathways between the LGN and

area MT, whereas those without did not (Ajina et al., [2015](#)). Therefore, a pathway involving K-cell LGN layers that bypass the striate cortex and terminate instead in extrastriate regions such as area MT may account for some preserved visual abilities in blindsight.

These two explanations for blindsight – the tectopulvinar and LGN-extrastriate explanations – are not mutually exclusive. Blindsight is rare, being observed in only a small number of patients, each of whom has a slightly different pattern of brain damage and even different perceptual experiences (Weiskrantz, [2004](#)). Some patients claim that they can see nothing in the blind field, whereas others report a vague sense of something “being there” while still denying that they can “see” it. Thus, different pathways may play a role in different patients.

This heterogeneity of patients allows for few generalizations at present, except that perhaps blindsight is supported by regions of the brain that are particularly sensitive to visual motion, as is the case both for the superior colliculus and area MT. A more philosophical question is why some kinds of visual processing, such as those supported by the striate cortex, seem to give rise to conscious experience while others do not. This question is much harder, and perhaps impossible, to address with scientific methods.

Divergence Into the “What” and “Where” Pathways

The complexity of the organization of visual regions in the brain can seem mind-boggling. Illustrating this complexity, [Figure 5.16](#) represents a preliminary sketch of anatomical connections between various visually responsive regions of the macaque cortex (Felleman and van Essen, [1991](#)). The human visual system is likely to be just as complex, if not more so. Amidst this complexity, researchers have identified two main routes along which information travels when it leaves the striate cortex (Bell et al., [2014](#)). Information from the striate cortex bifurcates, projecting both ventrally (i.e., downward) toward the inferior temporal cortex, and dorsally (i.e., upward) toward the parietal lobe (see [Figure 5.17](#)).

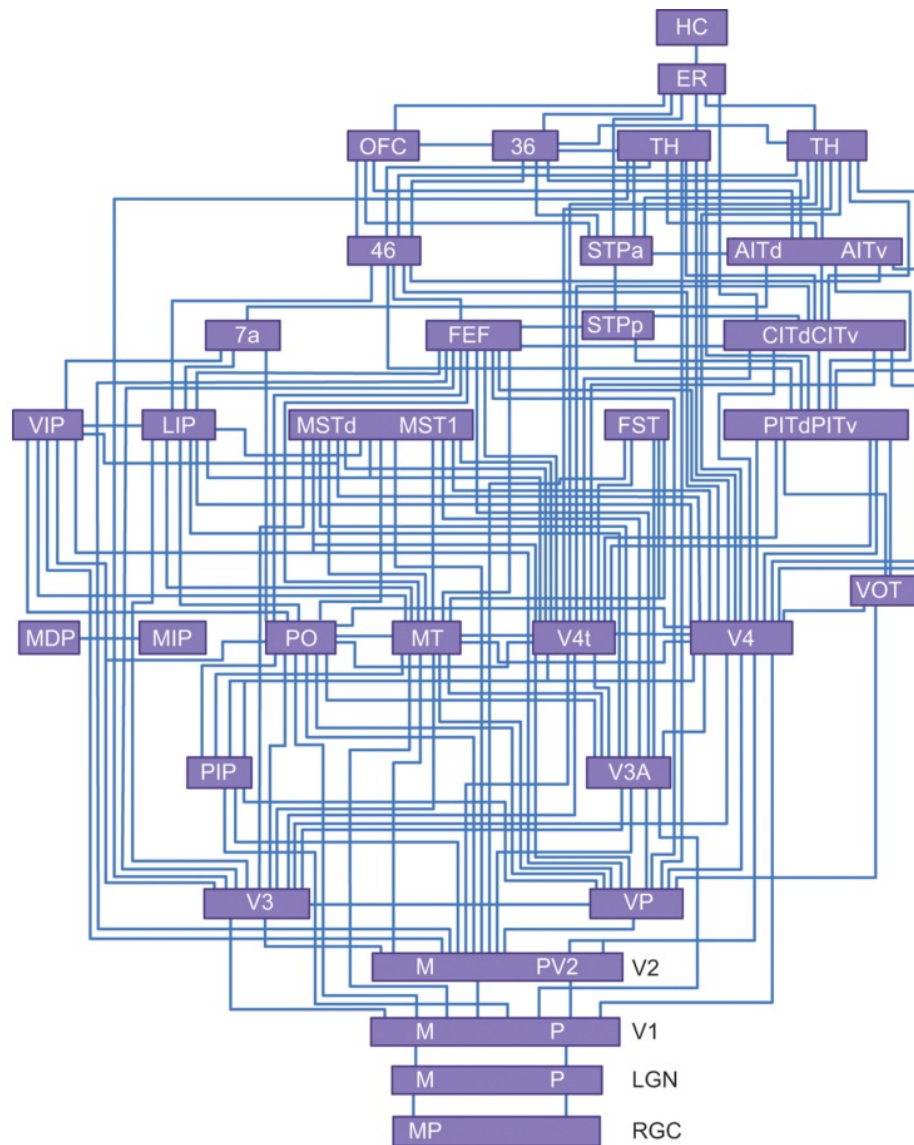


Figure 5.16 Illustration of the complexities of the visual cortex.

Each box is a separate cortical region that is known to play a role in vision, and the lines represent known pathways between these regions. These data are based on anatomical findings in the macaque monkey.

Source: Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*, 1, 1–47. Reprinted by permission of Oxford University Press.

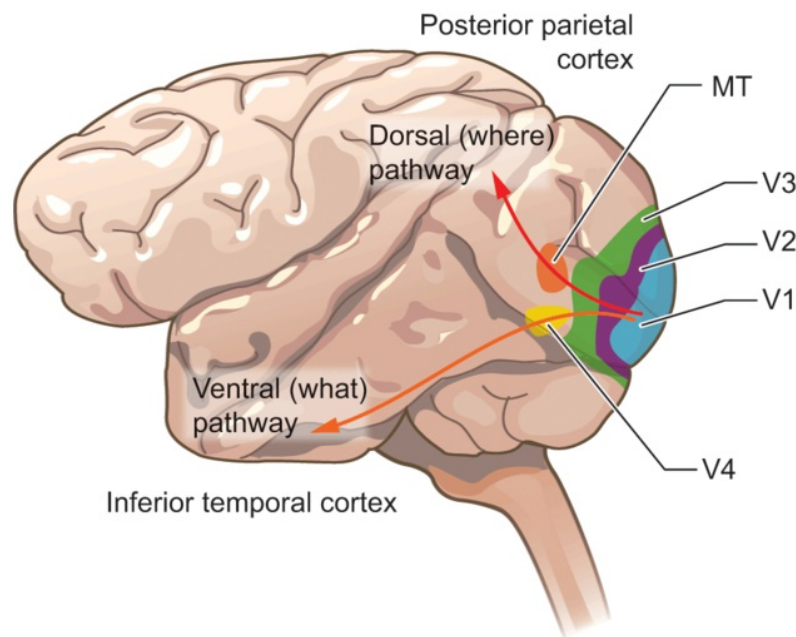


Figure 5.17 Illustration of dorsal and ventral streams for visual information.

As information travels along each of these two pathways out of striate cortex, the ventral and dorsal streams, it undergoes further transformations to serve the goals of higher-level vision. Each step along either pathway takes the information one step further away from the “raw materials” encoded by the retina and toward the higher-level, more abstract representations of the visual world that we will learn about in [Chapters 6](#) and [7](#). These two paths are thought to serve two distinct goals of visual processing: identifying objects (ventral stream) versus representing their spatial locations (dorsal stream). These functions are sometimes referred to as the “what” and “where” functions, answering the two main questions: “What kind of object am I looking at?” and “Where is it located in visual space?”

Original evidence for the dissociation between dorsal and ventral paths came from studies of monkeys with brain lesions (Mishkin et al., [1983](#)). Monkeys were trained to complete two different visual discrimination tasks, one that required understanding spatial locations and another that required understanding objects and shapes (see [Figure 5.18](#)). In the first task, monkeys viewed two food wells with identical covers, with a small tower situated closer to one of two wells. The position of the tower was moved

from one trial to the next, but on each trial the food was hidden in the well closest to the tower. Thus, to obtain the food, the monkey had to understand spatial positions. Damage to the parietal region (dorsal stream) disrupted performance on this task, whereas damage to the temporal lobe (ventral stream) did not.

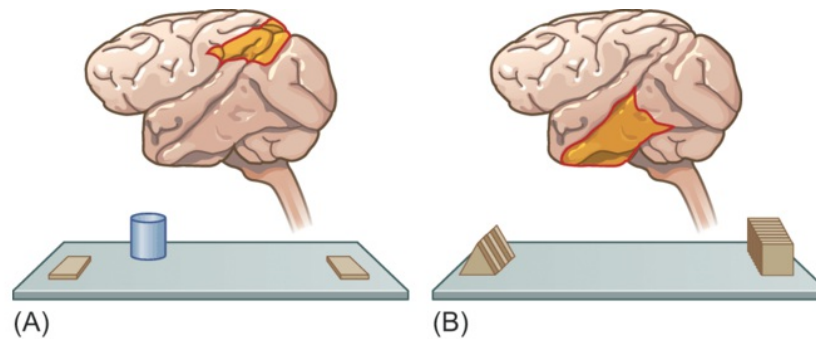


Figure 5.18 Tasks sensitive to dorsal versus ventral stream damage in monkeys.

(A) In the landmark-discrimination task, the monkey sees two identical food-well covers and a landmark. A reward is hidden in the food well closer to the landmark. The position of the landmark varies randomly from trial to trial, sometimes closer to the left food well and sometimes closer to the right well. When monkeys sustain bilateral damage to the posterior parietal region, shown in orange, they cannot perform this task. (B) In the object-discrimination task, the monkey sees two distinct food-well covers, one of which it has been familiarized with prior to the trial. A reward is hidden under the food-well cover that was not previously viewed. This task is known as a nonmatch-to-sample paradigm because the animal must choose the well covered by the object that was not viewed previously. When monkeys sustain bilateral damage to inferotemporal areas, shown in orange, they cannot perform this task.

In the second task, the monkey viewed an object (such as a striped pyramid) in a central location. This object was then placed over one food well, and another object (e.g., a checkered rectangle) was placed over the other food well. In each trial, the food was hidden under the novel object (in this case, the checkered rectangle). This procedure is known as a [nonmatch-to-sample paradigm](#) because in order to get the food, the monkey has to choose the item that doesn't match the previously shown sample

object. Normal performance on the task requires an ability to discriminate between the two shapes. Monkeys with temporal lobe damage performed poorly on this task, whereas those with parietal lobe damage performed normally. Thus, this elegant double dissociation provides evidence that dorsal and ventral streams are crucial for spatial understanding and object recognition, respectively.

Neuroimaging studies in humans confirm the basic dissociation between the dorsal and ventral pathways. For example, in one study, participants viewed pictures of objects presented on a screen (Marois et al., [2000](#)). On some trials, the object's identity changed (from a chair to a car, for example), and on other trials its spatial position changed. Although either type of change produced increases in activity in both ventral and dorsal stream areas, the magnitude of the increase depended on whether the identity or location had changed. As illustrated in [Figure 5.19](#), identity changes led to greater increases in lateral occipital and inferior temporal cortex activity compared to location changes, whereas location changes led to greater increases in superior occipital and posterior parietal cortex activity (see also Zachariou et al., [2014](#)).

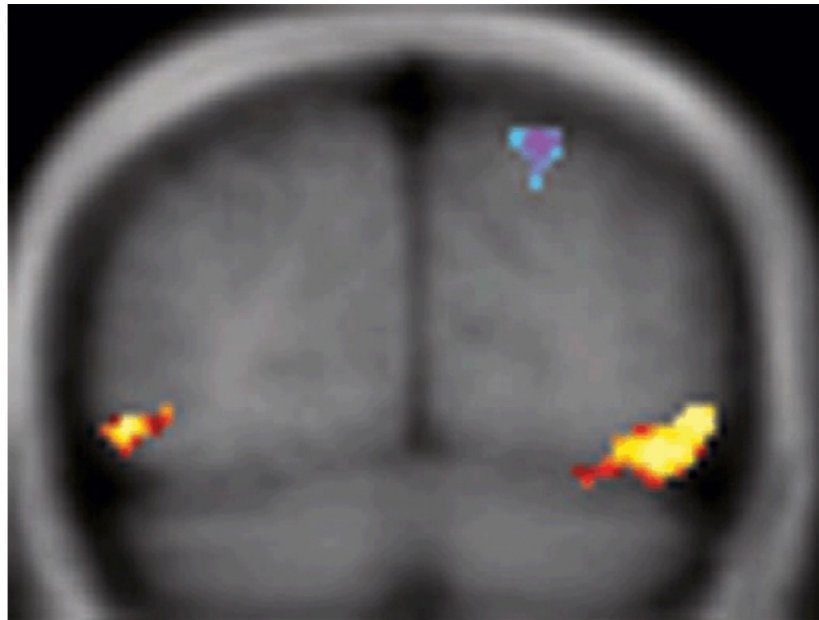


Figure 5.19 Dissociation between areas sensitive to object orientation and object identity.

In this study, participants viewed pictures of objects. On some trials, the object's identity changed, whereas on other trials, its spatial location changed. The figure shows the ventral stream area that was more activated by identity changes than by location changes (in yellow) and the dorsal stream area that was more activated by location changes than by identity changes (in blue).

(from Marois et al., [2000](#))

Although initial studies conceptualized the dorsal and ventral streams as “where” and “what” pathways, many researchers prefer to conceptualize the dorsal path as a “how” pathway rather than a “where” pathway, because it is closely linked with motor areas of the brain that govern how we act upon the visual world (Goodale and Westwood, [2004](#)). The functions of the ventral and dorsal paths will be covered in much more depth in [Chapters 6](#) and [7](#), which focus on object recognition and spatial cognition, respectively. At this point, it is useful to see these two paths as another example of parallel processing within the visual system.

Auditory Processing

Research on the neural bases of perception has long been dominated by studies of vision, because primates like us are known to have exquisite visual capabilities. But audition, the perception of sounds, is also a crucial sensory function of the primate brain and is essential for some relatively unique human capacities, such as language. Here we review some of the most important findings in research on the neural basis of auditory perception.

It can be useful to consider why we have both auditory and visual senses. What additional information about the world does audition provide that we can't get from vision? One obvious limitation of vision is that it is restricted to what your eyes are viewing. Vision gives you no information about what is going on behind you. Likewise, vision yields less information about what is happening far away, whereas sounds can travel some distance. Also, vision is not very useful at night. We evolved in a world where both dangers and opportunities could exist behind our backs, hidden in bushes, at far distances across the landscape, or under cover of darkness. Therefore, the ability to perceive sounds is an extremely advantageous complement to the ability to perceive patterns of light. Auditory processing is also essential to the perception of speech, which we will consider in detail in [Chapter 8](#).

Computational Problems in Audition

The auditory system must solve some of the same kinds of computational problems as the visual system. Different sensory features, such as the pitch, loudness, and timing of sounds, must be processed in order to recognize specific auditory events, like the sound of an alarm ringing or a child crying. This need to represent various features of the stimulus is similar to the visual system's need to represent features such as contrast, line orientation, brightness, and color. The brain constructs the representation of these important features from elemental inputs coded by sensory receptors. In vision, those elemental inputs consist of spots of light of varied wavelengths striking photoreceptors, whereas in audition, the elemental inputs consist of sound waves of varied frequencies stimulating the hair cells in the inner ear.

The auditory system, like the visual system, also has to be able to separate “figures” from their backgrounds. For example, visual perception allows us to discern an apple against the background of the whole tree. Similarly, auditory perception allows us to separate a single sound stream, such as a person’s voice, from the ambient background noise.

Auditory perception must also allow us to locate sounds in space, just as vision is concerned with the location of objects in the world. For example, it is useful to know whether the roar of that lion is coming from behind you or to your left. The problem of spatial localization is even more challenging for audition than for vision, because space is not coded directly on the initial array of sound receptors within the ear, whereas at least two dimensions of space are coded directly on the retina. Therefore, the brain must compute a representation of auditory space. As we will see shortly, computations necessary for spatial localization are initiated very early in the auditory system.

Organization of the Auditory Pathways

Auditory processing begins in the ear, as you probably suspected. The ear is a very complex organ (see [Figure 5.20](#)), and we will focus here only on its most important features. Within the inner ear is the **cochlea**, which contains the cells that translate sound energy into neural impulses. The cochlea is wound up into a spiral, and has a set of membranes that move in relation to one another when sound waves enter the ear. When these membranes move back and forth, the motion stimulates hair cells (see [Figure 5.21](#)). These cells have little hairs called cilia sticking out of them, and the movement of the cilia in response to sound vibrations ultimately causes the cell to emit graded potentials. Hair cells synapse on spiral ganglion cells, whose axons make up the auditory nerve, just as the axons of retinal ganglion cells make up the optic nerve.

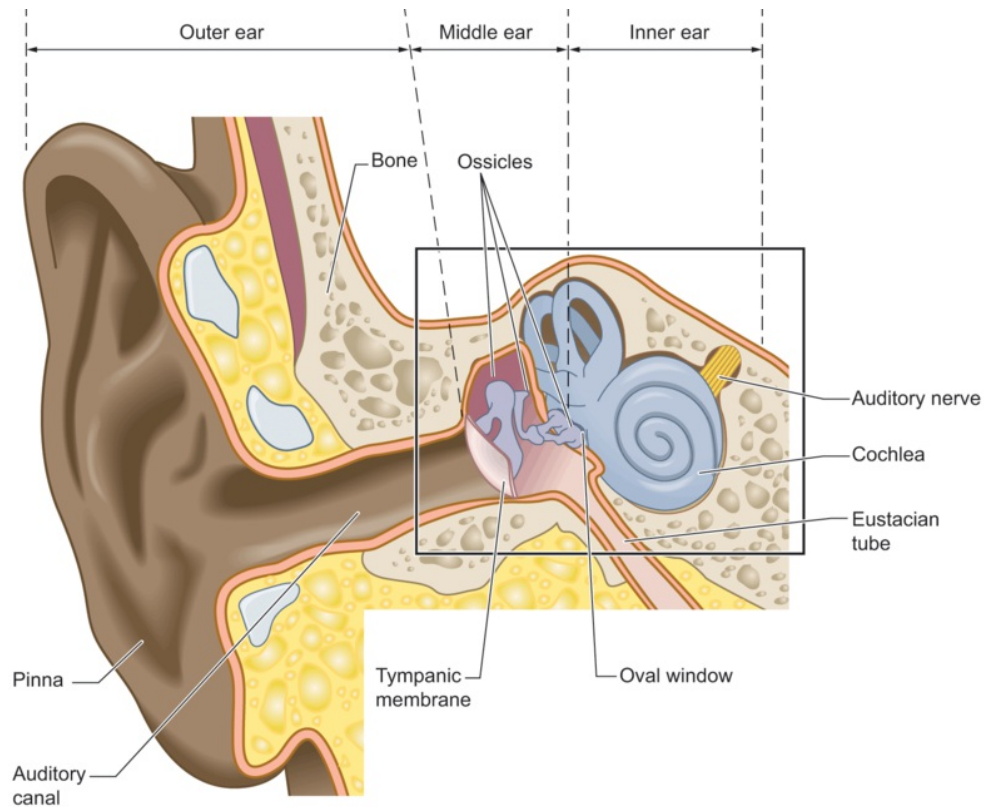


Figure 5.20 The anatomy of the ear.

Sound enters the ear canal both directly and by reflection off the pinna (outer ear). In the ear canal, sound causes vibration of the tympanic membrane, which in turn causes vibration of the bones (ossicles) of the inner ear. These vibrations are then transferred to the cochlea via the oval window.

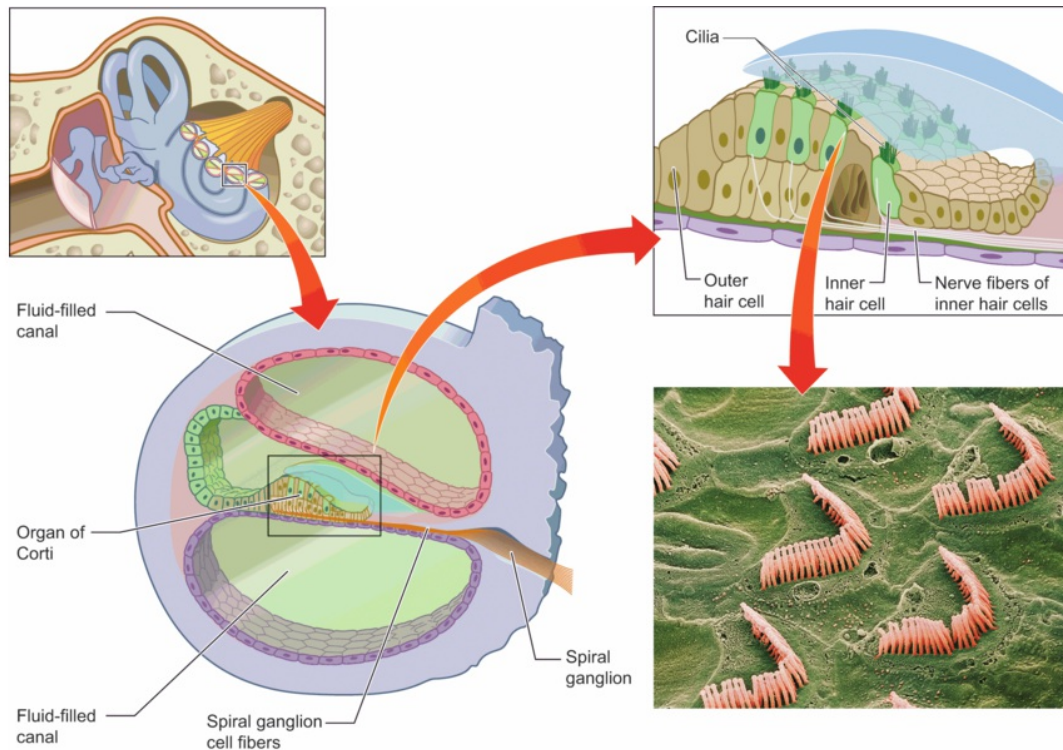


Figure 5.21 The cochlea.

Residing in the middle of the cochlea is the organ of Corti, which contains the hair cells that respond to sound. It is surrounded on both sides by fluid-filled canals that contain lymph-like liquid. Movement of the cilia of the inner hair cells is transduced into an electrical signal. This is relayed to spiral ganglion cells the axons of which form the basis of the auditory nerve.

Inset source: Science Photo Library.

Most importantly for our purposes, sound vibrations of different frequencies cause stimulation of different subsets of hair cells within the cochlea. That is, high frequencies stimulate a different set of hair cells than low frequencies. If you could unroll the cochlea, you would find that hair cells that are sensitive to high-frequency sound are located near the base of the cochlea, whereas those sensitive to low-frequency sound are located near the apex (tip) of the cochlea. Therefore, by knowing which sets of hair cells were stimulated, the brain can determine which frequencies are present in the sound. This organization creates a [tonotopic map](#), much the way that the pattern of light

across the retina forms a retinotopic map. In the case of audition, the map represents sound frequencies.

Auditory information passes through several stopover points on its way from the ear to the auditory cortex (see [Figure 5.22](#)). Two of these locations are in the brainstem. First, the auditory nerve synapses in the [cochlear nucleus](#) in the medulla, and from there a pathway sends the information onward to the [superior olivary nucleus](#), also in the medulla. Note that between the cochlear nucleus and the olivary nucleus, the pathway extends both contralaterally and ipsilaterally, such that information from both ears is shared with both left and right olivary nuclei. From there, the information travels to the [inferior colliculus](#) in the midbrain, and then onward to the [medial geniculate nucleus](#) of the thalamus. From there, the information is finally sent to the primary auditory cortex, which we discuss in more detail in a later section.

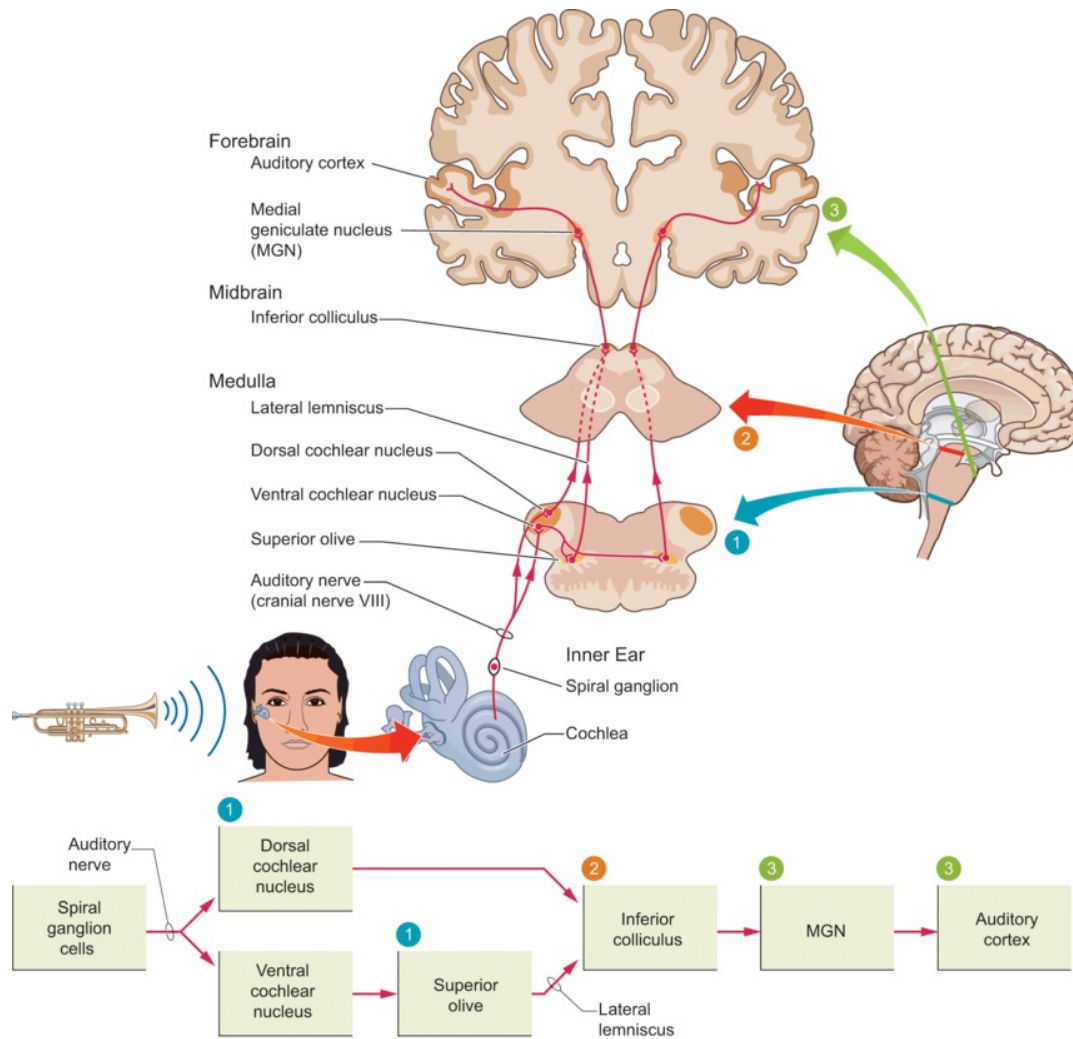


Figure 5.22 Auditory pathways from the cochlea to the cortex.

Information from the ear synapses at a variety of waystations in the medulla, midbrain, and thalamus on its route to the cortex. Notice that information from both ears first synapses on similar locations at the level of the brainstem, which provides a mechanism for determining the spatial location of sound.

At this point it is helpful to note both similarities and differences between the auditory and visual pathways. Some steps in these two pathways seem similar; for example, the inferior colliculus in the midbrain receives auditory information whereas (just above it) the superior colliculus receives visual information. The close proximity of the inferior and superior colliculi allows for some rudimentary audiovisual interactions that can assist in orienting to stimuli in the environment. Further, the medial geniculate nucleus of the thalamus receives auditory information, whereas the lateral

geniculate nucleus of the thalamus receives visual information, and both of these thalamic nuclei project to the primary sensory cortex for that modality.

Another feature that the auditory and visual systems share, to some extent, is the presence of descending projections. So far, we have focused on the ascending (upward) pathway, from the ear to the cortex. However, there are also descending (downward) projections that send modulatory influences all the way down each step of the auditory processing chain. In this way, top-down signals representing the effects of attention, expectations, and contextual factors can influence and shape the information that is proceeding upward in a feed-forward fashion from the ear to the cortex. These top-down projections may serve a function similar to that of the projections from the visual cortex to the LGN in the visual system.

Beyond these similarities, we can also see some differences between visual and auditory pathways. For example, there are more stopover points between the ear and the auditory cortex than between the eye and the visual cortex. This means that some computations may be going on in earlier stages, such as the brainstem, in the auditory system. Furthermore, auditory information from both ears is shared at the level of the brainstem, whereas visual information from both eyes is not integrated until the level of the visual cortex.

Brainstem Computation of Spatial Location

As mentioned earlier, the spatial location of a sound source must be computed by the auditory system, because the cochlea itself does not directly map spatial locations in the same way that the retina does. Here we discuss the informational cues that the auditory system can use to localize sounds, as well as evidence from other species that these computations can be carried out in the brainstem.

The fact that we each have two ears is essential to the ability to localize sounds. The auditory system calculates sound location by comparing the inputs from the two ears, just as the visual system calculates the dimension of spatial depth (which is not coded on the retina) by comparing inputs from the two eyes. Because the ears are located on

opposite sides of the head, a single sound source will have a different impact on each ear, depending on where the sound source is located. As illustrated in [Figure 5.23](#), a sound coming from the right side of your head will reach your right ear slightly before it reaches your left ear, a phenomenon known as [interaural time difference](#). The sound will also be louder when it reaches your right ear, because the head will block some of the sound from reaching the left ear; this phenomenon is known as [interaural intensity difference](#). Based on interaural (“between the ears”) differences in time and intensity, the auditory system can deduce the spatial location of a sound source. This computation requires exquisite precision in timing, because interaural time differences are typically less than 1 millisecond.

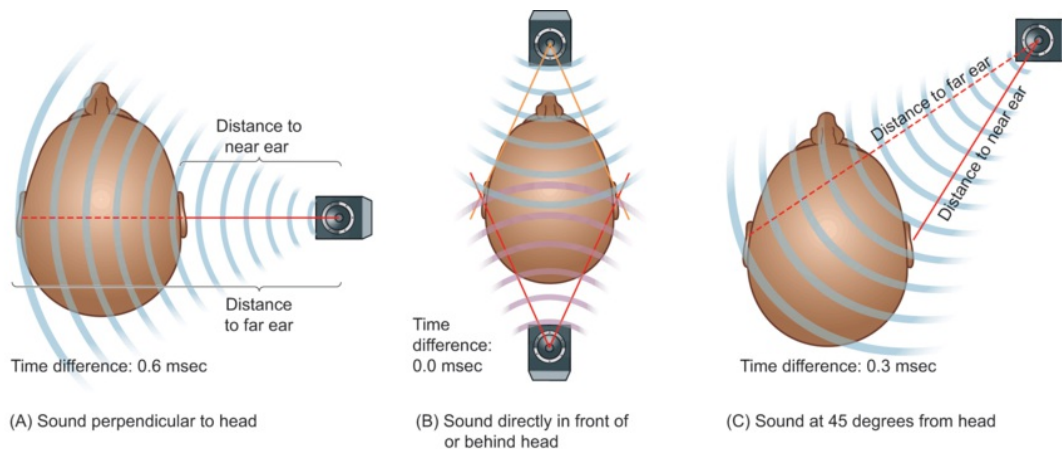


Figure 5.23 Localizing sound by comparing inputs from the two ears.

In (A), the sound reaches the right ear approximately 0.6 ms before it reaches the left ear. In (B), sounds either directly ahead or directly behind will reach the right and left ears simultaneously. It can often be difficult to tell whether a sound is coming from directly ahead or directly behind; luckily, turning your head a little can eliminate the confusion. In (C), the sound at about a 45-degree angle to the right will strike the right ear about 0.3 ms earlier than the left ear.

The auditory system also relies upon a more complex set of cues that reflect how sound is shaped by the head and ear. A sound coming from above and a sound coming from below will each be shaped differently by the structure of the outer ear, and these cues are analyzed by the auditory system to determine spatial location in the vertical

dimension. There is an easy way to demonstrate how much this shaping of sound by the outer ear influences your sound localization ability. Find a friend and ask him or her to shake some keys in front of you, either right in front, above, or below you while your eyes are closed. You should have no difficulty telling the location of the keys. Now try the same thing, but this time fold your ears over to block the ear canal, and notice what happens.

Evidence from other species suggests that brainstem structures are capable of basic computation of spatial location. Many studies have been carried out in species of predatory birds, such as owls, that have excellent spatial localization abilities (Konishi, [2003](#); Pena and Gutfreund, [2014](#)). Imagine an owl perched high on a tree branch at night, listening for the rustle of a small mouse far below. The owl needs to know exactly where the mouse is so that it can swoop down suddenly to catch its prey. Part of the owl's exceptional spatial localization may reflect species-specific adaptations – for example, the ears of an owl are tilted asymmetrically, one upward and one downward, to further aid in distinguishing sounds. However, much of what has been learned about the owl's brainstem computations regarding auditory space appears to apply to mammals as well (Schnupp and Carr, [2009](#)).

Brainstem areas compute spatial location in part by using so-called [delay lines](#) and cells called [coincidence detectors](#) that take into account the different arrival times of a sound at the left and right ears. A schematic depiction is shown in [Figure 5.24](#). The basic idea is that certain cells respond preferentially to particular timing discrepancies between signals from the two ears. To understand the concept of delay lines and coincidence detectors, consider this analogy. Imagine two runners whose starting positions are at opposite ends of a football field. If the two people start running toward one another at the same time (and at the same rate), they will meet in the middle, at the 50-yard line. However, if one runner gets a head start, the two runners will not meet in the middle. Rather, they will meet somewhere closer to the runner who started late, because the head start will allow the first runner to cover more distance. If you wanted to know which runner started first, you could simply look at where the runners met. If

they met at the 50-yard line, then you would know that the runners started at the same time. But if they met at the 25-yard line (three-quarters of the way down the field), you would know that one of the runners had a head start (and you would know which one).

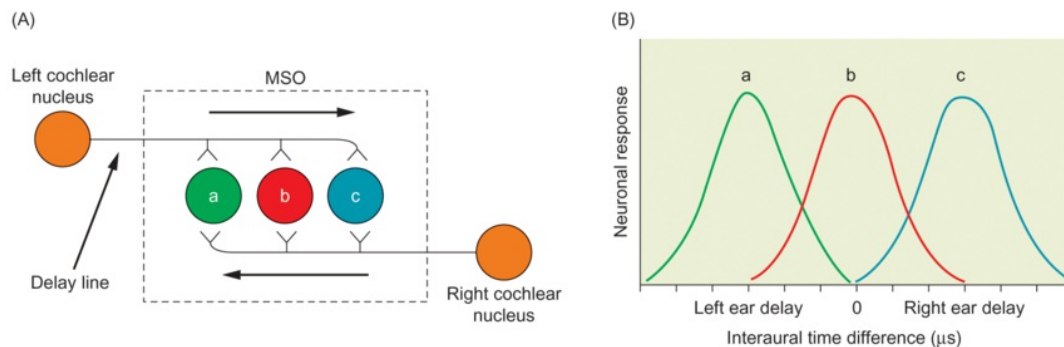


Figure 5.24 Model of delay lines and coincidence detectors in brainstem.

(A) Signals from the right and left cochlear nuclei are sent along axons, referred to as delay lines, in the medial superior olivary nucleus (MSO) in the brainstem. Cells in this nucleus (such as cells a, b, and c) are excited by simultaneous stimulation from both input lines. (B) Cells a, b, and c respond maximally to different interaural time differences. For example, cell a responds best when sound arrives first at the right ear, and then after a brief delay at the left ear. Such a scenario causes the inputs from the cochlear nuclei to arrive at the same time at cell a. In contrast, cell b responds best when the sound arrives simultaneously at the left and right ears, and cell c responds best when the sound arrives first at the left ear and then at the right ear after a short delay. Because interaural time differences are a cue to the location of the sound, these cells code for different sound locations.

Source: Cohen, Y. E., and Knudsen, H. I. (1999). Maps versus clusters: Different representations of auditory space in the midbrain and forebrain. *Trends in Neuroscience*, 22, 128–135. Reprinted by permission of Elsevier.

Now, imagine that instead of runners, there are sounds arriving at the two ears, and they are traveling toward one another not on a football field but as signals traveling along axons, “delay lines” that reach into the midbrain and make contact with a line of cells along their path. Imagine that each cell along the path is positioned in a spot

analogous to a yard line on the football field. Furthermore, each cell is stimulated by the traveling signal, and it is maximally stimulated when the signals from the right and left ears arrive at the cell simultaneously. Such cells are often referred to as coincidence detectors because they respond best to the coinciding of inputs from the two ears. A cell right in the middle of this path (equivalent to the 50-yard line in the football field example) would be maximally excited when the signals from the two ears started down their paths at the same time, because the two signals would meet each other at this middle cell in the series and they would both stimulate that cell simultaneously. But another cell, let's say one positioned analogous to the 25-yard line, would be most excited when the signal from one ear got a head start, because the head-start signal could get further along the pathway (toward the "25-yard line" cell) before it met up with the later-starting signal.

Essentially, knowing which of the coincidence detectors is maximally activated is equivalent to knowing where the left-ear and right-ear signals meet up along the delay lines, which in turn tells you which signal got a head start. Now remember that the "head start" represents the interaural time difference, which is a cue to the location of the sound. Logically, then, activity in cells along the delay lines codes for the spatial location of the sound source.

Through careful work with animal models such as the barn owl, researchers have determined that such coincidence detectors are present in the superior olivary nucleus (called the laminar nucleus in the owl), which is the first point at which information from the two ears can be compared (Konishi, [2003](#)) (refer back to [Figure 5.22](#)). Thus, at the level of the brainstem, a map of auditory space is essentially computed by comparing the inputs from the two ears. Subsequent steps in the auditory processing sequence make further use of this spatial location information. For example, the inferior colliculus also contains a map of auditory space that is then integrated with the visual map of space in the superior colliculus. Intuitively, it makes sense that spatial location

would be coded very early in the processing stream, because it is so important for rapid response to auditory events.

The delay-line model is an elegant computational model explaining how spatial location can be coded rather simply. Of course, the more you think about it, the more you will realize that things can't be quite so simple. For example, let's say that you hear a low-pitched sound to your left, but a high-pitched sound to your right. How can the auditory system identify their separate spatial locations if both signals are traveling along the delay lines? One clue is that there are multiple delay lines in the olivary nucleus, each corresponding to a different sound frequency. Hence, the low-pitched sound is processed through a different set of coincidence detectors than the high-pitched sound, allowing each sound to be localized separately. In addition, as mentioned previously, the brain can use interaural intensity (loudness) differences as well as interaural time differences as a cue to location. Interaural intensity differences also appear to be coded by the olivary nucleus, albeit by a different sector of that nucleus than timing differences. Finally, the brain can also use more complex cues, such as the changing composition of the sound as it bounces around either the left or right outer ear. The neural coding of these more complex spatial location cues is not currently well understood.

Organization of Auditory Cortex

Once auditory information has ascended through subcortical paths, it arrives at the auditory cortex, just beneath the Sylvian fissure in the temporal lobe. The layout of auditory cortex has been studied in other mammals, including primates, through single-cell recording. Neuroimaging studies in humans have also addressed the organization of auditory cortex, although studying auditory perception in a neuroimaging environment poses some challenges. For example, the machinery required to conduct fMRI studies can generate a lot of noise. In addition, it can be difficult to create naturalistic sounds (e.g., sounds perceived as coming from various distances) within the constraints of a magnetic resonance imaging system. Nevertheless, studies in humans and other species

generally converge on a few key principles of auditory cortex organization (Recanzone and Sutter, [2008](#)).

First, auditory cortex can be subdivided into a few regions, illustrated in [Figure 5.25](#). These regions are called the **core**, the **belt** (which surrounds the core), and the **parabelt** (which surrounds the belt) (Hackett and Kaas, [2004](#); Romanski and Averbeck, [2009](#); Woods et al., [2010](#)). The core itself can be further subdivided into areas A1 (primary auditory cortex) and regions anterior to A1, referred to as the rostral and rostrotemporal fields. The core region receives input from the medial geniculate nucleus, whereas the belt region receives most of its input from the core, and the parabelt receives input from the belt. So, there appears to be a rough hierarchy extending from the medial geniculate to the core, then to the belt, then to the parabelt. However, the belt and parabelt regions also receive some direct input from the medial geniculate, so the hierarchy is not completely rigid.

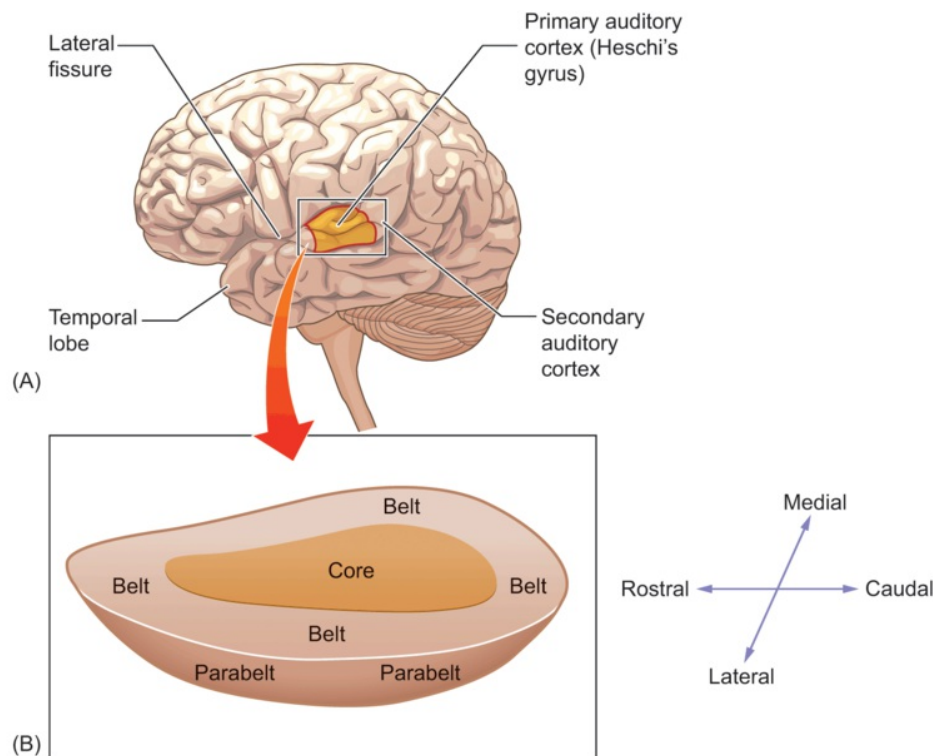


Figure 5.25 Auditory cortex.

This representation of auditory cortex in the macaque monkey includes the central core area, surrounded by the belt and parabelt.

All three of the areas within the core contain tonotopic maps. [Figure 5.26](#) illustrates a tonotopic map within area A1. A [tonotopic map](#) is somewhat analogous to a retinotopic map in the visual cortex, in the sense that they both map out certain features of the sensory world in a systematic way. However, whereas a retinotopic map is essentially a map of space (i.e., a map of the retina), the tonotopic map is not a map of space. Rather, it is a map of sound frequencies. The frequency of a sound refers to how fast sound waves oscillate, and roughly corresponds to our perceptual experience of pitch; high-frequency sounds are perceived as high pitches, and low-frequency sounds as low pitches. In primary auditory cortex, each cell responds best to a certain frequency of sound, and neighboring cells respond to similar frequencies. In a sense, the tonotopic map is a map of the cochlea, because the cochlear cells are also organized by frequency.

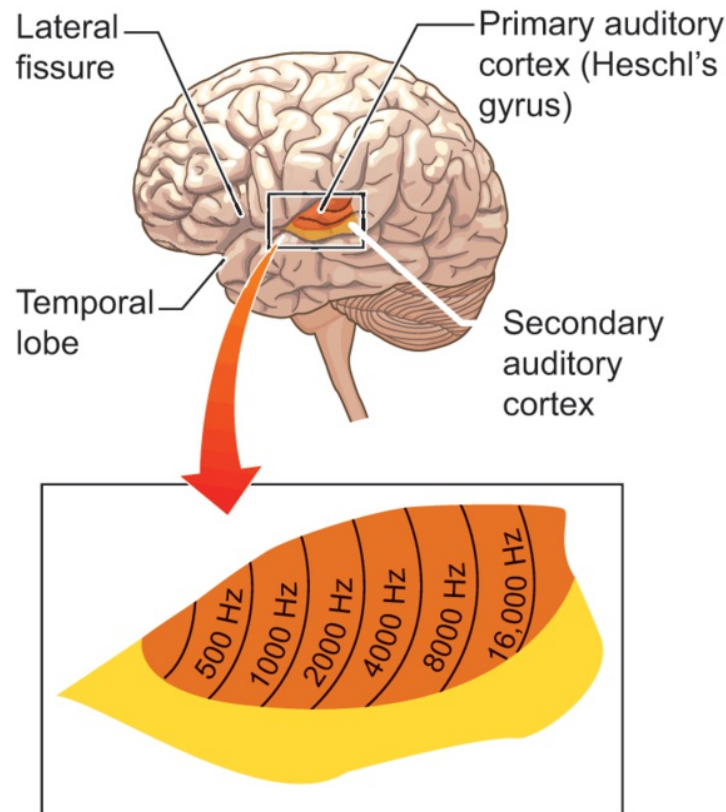


Figure 5.26 Tonotopic mapping in auditory cortex.

Cells that are all maximally responsive to the same frequency are localized in similar bands or regions. Note that cells maximally responsive to lower frequencies are located more rostrally, whereas those responsive to higher frequencies are located more caudally.

Cells in a tonotopic map can be thought of as having receptive fields, but these receptive fields are not spatially defined as in the visual system. Rather, individual cells have preferred sound frequencies, such that only frequencies within a particular range will excite the cell; other frequencies will produce no response from the cell. For each cell, we can create a graph that shows the cell's sensitivity across different sound frequencies (see [Figure 5.27](#)). This graph is often referred to as the cell's [tuning curve](#).

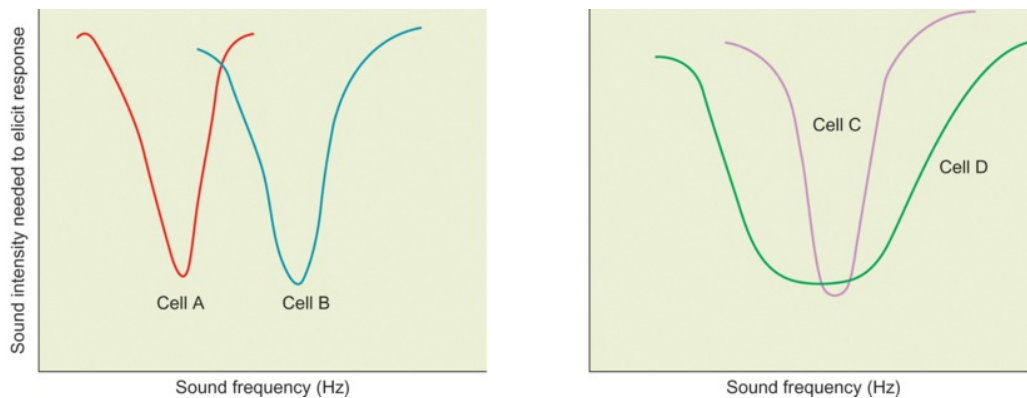


Figure 5.27 Tuning curve of auditory cortex cells.

This figure schematically illustrates the sensitivity of hypothetical auditory cortex cells to different sound frequencies. The curve represents the sound intensity that is needed to provoke a response from each cell, as a function of the sound frequency. The low point on the curve indicates the sound frequency to which the cell is most responsive. Cell A is more responsive to lower sound frequencies than cell B; cell C has a sharp tuning curve, whereas cell D has a shallow tuning curve.

Cells in different parts of the auditory cortex have different kinds of tuning curves. Within area A1, cells are sharply tuned to specific frequencies, whereas in the belt and parabelt regions, cells are more broadly tuned, responding to a variety of stimulus frequencies. In A1, cells also tend to respond best to pure tones (tones composed of only one frequency), whereas in the surrounding regions, cells tend to respond best to more complex stimuli that incorporate several individual sound frequencies. If the belt and parabelt areas are damaged in monkeys while the core is left intact, the monkeys are able to detect individual sounds, but they have difficulty recognizing complex patterns, such as tone sequences (Kaas et al., [1999](#)).

Other studies in monkeys have shown that cells within the lateral belt area are especially responsive to the sounds of monkey vocalizations (Romanski and Averbeck, [2009](#); see also Petkov et al., [2008](#); Ortiz-Rios et al., [2015](#)). In addition, cells in the belt area appear to be more susceptible to top-down influences, such as where someone is directing attention, than those in the core (Atiani et al., [2014](#)). Thus, as in the visual

system, there is a hierarchy in which early cortical stages seem to represent simpler features, whereas later cortical stages represent more complex combinations of features.

In humans, the lateral belt and parabelt regions are thought to correspond to the [planum temporale](#), an anatomical region that is known to be especially important in speech perception. The planum temporale on the left side of the brain is activated by speech sounds, while this region of the brain in both the left and right hemispheres is also activated in response to other complex auditory stimuli like sound patterns, music, and environmental sounds (Griffiths and Warren, [2002](#)). Thus, this region seems crucial in auditory pattern recognition.

One hypothesis about the organization of auditory cortex proposes that spatial and nonspatial features of a stimulus are handled in somewhat separate streams (Rauschecker, [2015](#)). According to this idea, information about spatial location is processed in more caudal/posterior regions of the auditory cortex, whereas nonspatial features are represented in more rostral/anterior sectors of auditory cortex. Nonspatial features could include particular patterns of sound frequencies that allow for the identification of a voice or recognizable nonvocal sound (e.g., bell chiming, phone ringing). This organization is analogous to the “what” and “where” segregation of function in the visual system.

Some evidence for “what” versus “where” segregation is found in the anatomical projections of the auditory cortex. Caudal auditory cortex projects to areas known to be important in spatial localization and sensory-motor integration, such as the parietal cortex and frontal eye fields, whereas rostral auditory cortex projects to association areas of the temporal lobe and orbitofrontal regions (Hackett and Kaas, [2004](#)). In addition, recordings from single cells in the monkey offer some support for this notion. Researchers recorded the activity of cells in the lateral belt region of auditory cortex while monkeys listened to communication calls from other monkeys. Cells in the anterior portion of the belt were more responsive to the specific type of call, whereas cells in the posterior region of the belt were more sensitive to the spatial location (Tian et al., [2001](#); see also Kuśmierek and Rauschecker, [2014](#)).

Some imaging studies in humans have also provided evidence for a dissociation between auditory spatial localization versus auditory object recognition. For example, one study combined fMRI and MEG results to examine this distinction (Ahveninen et al., [2006](#)). Participants heard a vowel emanating from a specific location in space. Next they heard a target that was either an identical item, a different vowel from the same location, or the same vowel in a different location. Posterior regions of both Heschl's gyrus and the superior temporal gyrus responded more when the items differed in spatial location than when they were different vowels, suggesting that these regions are sensitive to the location of the sound. In contrast, anterior regions of both Heschl's gyrus and superior temporal gyrus responded more when the items differed in the vowel presented rather than spatial location, suggesting that these regions are more sensitive to a sound's identity.

Furthermore, applying TMS to the posterior auditory cortex disrupted sound localization more than sound identification, whereas TMS to the anterior auditory cortex had the opposite effect, again providing evidence for a “what” versus “where” dissociation (Ahveninen et al., [2013](#)). Generally, it does seem that the auditory system, like the visual system, features parallel pathways that handle different aspects of the problem of perception.

Auditory-Visual Interactions

We tend to think of auditory and visual processing as taking place in largely separate streams within the brain, but at some point sounds and sights must be associated with one another. Such integration is necessary to associate the visual image of your dog, for example, with the sound of his bark. In a traditional hierarchical model, this multisensory integration was thought to take place at higher-level association regions of the brain, such as the association cortex in the temporal and parietal lobes. According to this convergent model, auditory and visual inputs are first processed in their separate cortical areas, and then those areas converge upon higher-level association areas.

Although this model clearly and accurately captures many aspects of multisensory integration, recent studies imply that interactions between auditory and visual processing can take place at earlier stages. According to interactive models, processing in one sensory modality (e.g., vision) can influence the information that is being simultaneously processed in another modality (e.g., audition).

An example of multisensory processing in auditory cortex comes from a study that examined responsiveness to vocalizations in monkeys (Ghazanfar et al., [2005](#)). Researchers recorded signals from populations of cells in the core and belt regions of monkey auditory cortex while the monkey either heard the sound of another monkey's grunt, viewed a silent video of the other monkey making the grunt sound, or heard the grunt together with the video. Not surprisingly, the sound without video activated cells in the auditory cortex, whereas the video without any sound did not activate auditory cortex cells. Most interestingly, though, the response of auditory cortex cells to the sound was altered by the simultaneous presence of the video. Some cell populations showed an enhanced response when the grunt sound was accompanied by the video, and others showed a suppressed response (see [Figure 5.28](#)). Thus, cells in auditory cortex are influenced by visual information. Future research will help to determine whether such visual influences on auditory processing are due to direct connections between unimodal visual and auditory cortical areas, or whether they are due to descending projections from multi-modal areas (such as temporal and parietal association areas).

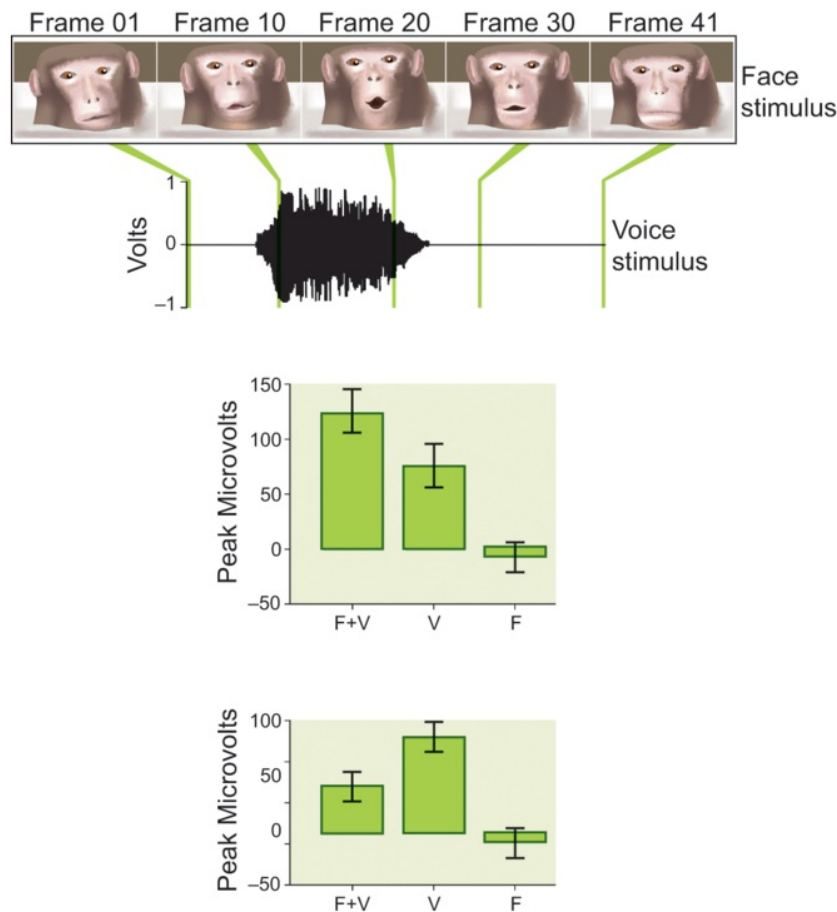


Figure 5.28 Effect of audiovisual stimulation on the response of auditory cortex cells in the monkey.

In this study, monkeys either heard a vocalization (voice alone – V), viewed a silent video of the monkey making that vocalization (face alone – F), or heard the vocalization along with the video (face + voice – F + V). One type of auditory cortex cell, shown on the top histogram, exhibited an enhanced response when the voice and face image were presented together, compared to the voice alone. Another type, shown on the bottom, exhibited a reduced response when the voice and face image were presented together, compared to the voice alone.

While the study just discussed focused on visual influences on auditory processing, it is also possible for auditory information to affect visual processing. Primary visual cortex (V1), particularly the region that represents the peripheral visual field, receives anatomical projections from auditory cortex (Falchier et al., [2002](#)). In addition, V1 cells are responsive to auditory information in at least some circumstances. One study

recorded the activity of V1 cells in a task in which a monkey had to orient its gaze to a stimulus in the periphery (Wang et al., [2008](#)). Cells in V1 responded more quickly to a combined audiovisual stimulus than to a solely visual stimulus. However, the auditory information had no effect on V1 responses when the monkey simply sat passively during the task rather than being required to orient its gaze. These findings suggest that audiovisual interactions in V1 may occur only when multisensory integration is functionally useful for performing a task. Studies in humans also indicate that auditory information can influence processing within the primary visual cortex (e.g., Feng et al., [2014](#)).

Other studies have examined multi-modal integration in brain regions that lie beyond the primary sensory areas, specifically regions that receive convergent input from auditory and visual areas. One example of this approach is research on multi-modal coding in the ventrolateral prefrontal cortex (VLPFC; see Romanski, [2012](#), for review). Although the VLPFC is primarily involved in controlling motor functions, some cells within this region appear to be responsive to combinations of sensory information that are important for communication.

Organization of the VLPFC at first seems to be segregated by sensory modality, as cells in one subregion of the VLPFC of the monkey are especially sensitive to the sounds of other monkeys' vocalizations, and cells in an adjacent subregion are especially responsive to images of monkey faces. But by recording from cells in both these areas while presenting audio only, visual only, and combined audiovisual stimuli, researchers found that some cells in VLPFC are multisensory (Sugihara et al., [2006](#)). For example, a cell that is primarily visual, responding maximally to a monkey face, may modulate its firing rate when a monkey vocalization is simultaneously presented. Likewise, a cell that is primarily auditory, responding maximally to a monkey voice, may modulate its firing rate when a face is presented along with the voice.

Interestingly, audiovisual combinations that did not involve faces or voices (such as pictures of random dots paired with hand claps) did not excite the cells as much as face-voice pairings. These results are especially exciting because the ventral frontal

lobe is known to be important in language production, as we will discuss in more detail in [Chapter 8](#). Thus, one function of multisensory integration in the VLPFC may be to facilitate communication (Romanski, [2012](#)).

Though there is still much to be learned about how the sensory modalities interact, it now seems clear that there are several possible mechanisms for their interaction, from the midbrain superior colliculus to the primary sensory cortex to higher-level multi-modal integration areas. Ultimately, such studies will help us to understand the neural basis of multi-modal perceptions, which are central to our everyday experience in which sights and sounds are perceived together seamlessly.

Conclusions

Both the auditory and visual systems must extract meaningful information from a massive amount of ever-changing input, whether it be patterns of light or sound waves. As we have seen, both sensory systems tackle these problems through a combination of serial processing, in which information ascends through a hierarchy of successive stages, and parallel processing, in which different processing streams are specialized to handle different aspects of the sensory stimulus. The representation of light and sound patterns (along with other sensory information such as smell, touch, and taste) allows us to understand the surrounding environment and forms the essential raw materials for other processes such as memory and language. In the next two chapters, we focus in more detail on brain systems involved in recognizing objects and understanding the spatial structure of the world around us.

Summary

The Retina

- The retina is derived from neural tissue and processes visual information before that information reaches the brain.

Photoreceptors

- Rods and cones are cells that contain light-sensitive pigments. Absorption of light by these pigments produces a neural signal that is communicated to other cells in the retina.
- Rods and cones have different pigments. The three cone pigments are sensitive to different wavelengths of light, thereby supporting color vision.
- Rods are distributed in the periphery of the retina, whereas cones are distributed in the center or fovea.
- Rods have a higher degree of convergence onto ganglion cells than do cones. This summation in the rod system allows detection of low light levels but loses information about precise location.

Ganglion Cells

- Ganglion cell bodies are located in the retina, and their axons make up the optic nerve.
- M ganglion cells are sensitive to motion and coarse patterns, whereas P ganglion cells code for color and finer details.

Receptive Fields

- A cell's receptive field refers to the region of space which, when stimulated with light, results in a change in the cell's firing rate.
- Photoreceptors have receptive fields that correspond to simple spots of light at certain locations in visual space.
- Ganglion cells have receptive fields with a center-surround organization, in which light located in a central spot in the visual field will have a different effect on the cell's firing than light located in the donut-shaped surrounding area. This

center-surround organization makes the cells especially excited by contrast between light and dark.

Pathways From the Retina to the Brain

- There are two main paths out of the retina. The tectopulvinar pathway extends from the retina to the superior colliculus in the midbrain, whereas the geniculostriate pathway extends from the retina to the lateral geniculate nucleus in the thalamus.

Lateral Geniculate Nucleus

- The LGN is a stopover point that organizes incoming information from the retina and sends it to the cortex.
- The LGN has a complex structure, with six layers that each contain a retinotopic map. Two layers, called magnocellular layers, receive input from M ganglion cells. Four other layers, called parvocellular layers, receive input from P ganglion cells. Magnocellular layers are important for motion perception, whereas parvocellular layers are important for color and form perception.
- The LGN receives massive feedback projections from the visual cortex, allowing the cortex to shape the information that is streaming in through the LGN.

Primary Visual Cortex (Striate Cortex)

- The striate cortex is the first cortical region to receive visual information.
- The striate cortex in each hemisphere contains a retinotopic map of half of the visual world.
- Cells in the striate cortex have different kinds of receptive fields than cells in the retina or LGN. Simple cells respond best to bars of particular orientations,

complex cells respond best to oriented bars moving in particular directions, and hyper-complex cells respond best to oriented bars of particular lengths.

- The striate cortex contains cells that are sensitive to certain amounts of binocular disparity, or discrepancy between left-eye and right-eye images. Binocular disparity information is important in coding for depth.

Contextual Modulation of Cells in Striate Cortex

- Cells in the striate cortex can change their firing rates depending on the surrounding context. This may help explain the well-known contextual influences on perception, and is likely due to top-down input from higher cortical regions as well as lateral connections within the striate cortex.

Visual Areas Beyond the Striate Cortex

- Multiple retinotopic maps exist in extrastriate cortex, including in areas V2 and V3. The unique function of each separate map is not well understood.
- Regions on the ventral surface of the brain are especially activated by color stimuli, and damage to these regions can lead to deficits in color vision, called achromatopsia. Controversy persists about whether these brain areas are true “color modules” and how they correspond to monkey visual area V4.
- From the striate cortex, two main paths emerge. The ventral path extends toward the inferior temporal lobe and is concerned with object recognition, whereas the dorsal path extends toward the parietal lobe and is concerned with spatial perception and action.

Blindsight

- Patients with blindsight exhibit some rudimentary visual capacities even though they experience being blind in the affected visual field.

- There is controversy about whether residual vision in blindsight is due to an intact tectopulvinar path or an intact path from the LGN to extrastriate areas.

Auditory Processing

- The auditory system must solve computational problems similar to those of the visual system, including representing multiple features of the sensory world so that objects and their locations can be understood.
- The auditory pathway begins at the cochlea in the inner ear, and extends to the cochlear nucleus in the medulla, the superior olivary nucleus in the medulla, the midbrain inferior colliculus, the medial geniculate of the thalamus, and auditory cortex.
- Spatial location can be computed at the level of the brainstem by comparing the timing and intensity of sounds that arrive at the left and right ears.
- The auditory cortex contains a primary auditory processing area within the core, as well as secondary processing areas known as the belt and parabelt. Primary auditory cortex appears to code simpler features, such as the frequencies of pure tones, whereas secondary areas code for more complex sound patterns.
- Researchers have proposed a distinction between “what” and “where” processing pathways within the auditory cortex, but this distinction seems to be less clear-cut than in the visual system.
- Auditory and visual information processing streams can intersect with one another at several points, including the superior colliculus in the midbrain, the primary sensory cortices, and higher-level multi-modal cortical regions.

Chapter 6

Object Recognition



[The “What” Ventral Visual System](#)

[Deficits in Visual Object Recognition](#)

[Apperceptive and Associative Agnosias](#)

[Prosopagnosia: Agnosia for Faces](#)

[Category-Specific Deficits in Object Recognition](#)

[Theoretical Issues in Visual Object Recognition](#)

[Sparse Versus Population Coding for Objects](#)

[The Problem of Invariance in Recognition](#)

[Feature-Based Versus Configural Coding of Objects](#)

[Category Specificity: Are Some Types of Stimuli More Special Than Others?](#)

[Evidence From Other Primates](#)

[Evidence From Prosopagnosia](#)

[Evidence From Brain Imaging Studies](#)

[If Faces Are Special, Why Are They Special?](#)

[Bodies, Places, and Words Are Special Too](#)

[Object Recognition in Tactile and Auditory Modalities](#)

[Agnosias in Other Modalities](#)

[Tactile Object Recognition](#)

[Auditory Object Recognition](#)

What Versus Where Across Modalities

In Focus: Visual Imagery: Seeing Objects With the Mind's Eye

Summary

One crisp autumn night, Betty is yearning for a midnight snack when she remembers that some deliciously spiced tart apple pie is sitting in her refrigerator. She thinks, "That would be wonderful right now with a hot cup of tea!" Although for most people getting the pie out of the refrigerator and making a cup of tea would be simple, for Betty it will be a difficult task.

She walks into the kitchen and identifies the refrigerator by its large size and black color. But now she knows that she must find the pie, and that doing so will not be easy. As she peers inside the refrigerator, she sees a large, round object but deduces from its red color that it must be the leftover pizza pie, not the apple pie. Searching a bit more, she sees a tan, round-shaped object and reaches for it. But alas, as soon as she feels how flexible it is, she realizes that it's the package of tortillas, not the desired pie. Searching some more, she spies another tan, round-shaped object. This one feels stiff, like a pie pan, and is covered with plastic wrap. She pulls it out, takes off the plastic wrap, and sniffs. Ah, it is the pie she has been searching for! She carefully places it on the breakfast table.

Now for the cup of tea. Because Betty knows that the stove is to the left of the refrigerator, her usual strategy is to leave the teakettle sitting on the stove so that she can easily find it. Unfortunately, it's not there. "Ah," she sighs, "why didn't I just put the teakettle back where it belongs?" Now she begins to feel all the objects on the counter next to the stove. Hmm, that one feels tall and thin and a little greasy – must be the bottle of olive oil. Another one feels cylindrical and as if it's made of paper – must be either the large container of salt or the carton of oatmeal. Soon thereafter, she feels the distinctive curved arm of the teakettle and its wide, round body. Next to it, she feels the box of tea bags. That was

fortunate, she thinks, or I would have spent the next five minutes searching for the tea bags. She carefully places the box of tea bags on the stove; the box is now easily identifiable because its bright green color stands out against the white stove.

She then turns around to the sink, which she knows is located directly across from the stove, and fills the teakettle with water. Waiting for the water to boil, she puts her hand in the silverware drawer, feels for the tines of a fork, and takes one out. Soon, the teakettle whistles. She makes her cup of tea, walks over to the breakfast table, and gets ready to eat her piece of pie. That was a bit of a trial and tribulation, she thinks, but after the first bite of pie and sip of tea, she knows that all her effort was worthwhile.

At this point, you are probably wondering what strange disorder this woman has. As you think about this story, a number of possibilities may come to mind. Maybe she has a visual problem and is blind. This seems unlikely. She recognized the pizza (if only by its distinctive round shape and red color) and incorrectly grabbed an item that looked similar to the apple pie, a package of tortillas, rather than something quite different in shape and size, like a milk carton. Another possibility is that she has a memory problem and can't remember where things are located or the specific attributes of an item. This possibility seems unlikely, too. She remembered the locations of the stove and the sink. Furthermore, her memory for specific items must be intact because she recognized the apple pie as soon as she smelled it and the kettle as soon as she felt it.

This woman's neurological syndrome is not due to a problem in basic aspects of visual perception or memory. Her disorder is visual agnosia, a syndrome that deprives a person of the ability to use information in a particular sensory modality (in this case, vision) to recognize objects. The goal of this chapter is to examine the neural mechanisms that allow people to recognize objects through vision as well as other

senses. Our discussion concentrates on visual object recognition because it has been better studied than recognition through other senses.

The brain faces a number of difficult problems when attempting to recognize a visual object. The most basic of these is that the brain must form a three-dimensional representation of objects in the world from the two-dimensional information that falls on the retina. Thus, the brain must construct or add in information about an object's depth. But there are additional problems as well. One major problem is that items must be recognized no matter where they fall on the retina and no matter how much of the retina they fall upon. For example, a cat sitting in your lap projects onto a much larger area of your retina than a cat sitting on a chair across the room. Yet, in both cases, you must recognize the object as a cat. In addition, objects must be recognized regardless of their orientation. You must recognize a cat regardless of whether the cat is facing you with its eyes clearly visible or facing away from you so you see the back of its head. Finally, you must recognize an object as the same even when it appears in different configurations. Your brain needs to recognize that a cat sitting on its haunches, facing forward, is the same object as the cat lying curled up in a ball. In sum, although the same object can project upon the retina in various ways, the brain must nonetheless interpret the object as being the same, regardless of variations in retinal size, retinal position, orientation, and configuration (see DiCarlo et al., [2012](#)).

As discussed briefly in [Chapter 5](#), the ventral stream in the visual cortex is primarily concerned with recognizing objects through vision. In this chapter, we first discuss some of the basic characteristics of the ventral stream in humans and other primates. We then consider what can be learned about object recognition from the study of people who have agnosia, or object-recognition deficits. The chapter then turns to major theoretical questions in the study of object recognition, including how complex objects are represented by patterns of neural firing, how the brain is able to recognize objects under many different kinds of conditions, and whether there are parts of the ventral stream that are specialized for certain categories of visual objects, such as faces.

The “What” Ventral Visual System

Information departing from primary visual cortex is funneled into two distinct processing streams, one that courses ventrally toward anterior temporal regions and one that courses dorsally toward parietal regions. The [ventral visual processing stream](#) consists of the areas of the occipitotemporal and temporal regions that are devoted to processing visual stimuli. In the primate brain, the ventral stream is essentially synonymous with the inferotemporal cortex, which can be divided into three main segments: the posterior, central, and anterior inferotemporal cortex ([Figure 6.1](#)). These regions receive information flowing from the primary visual cortex (V1) via extrastriate regions such as V2, V3, and V4.

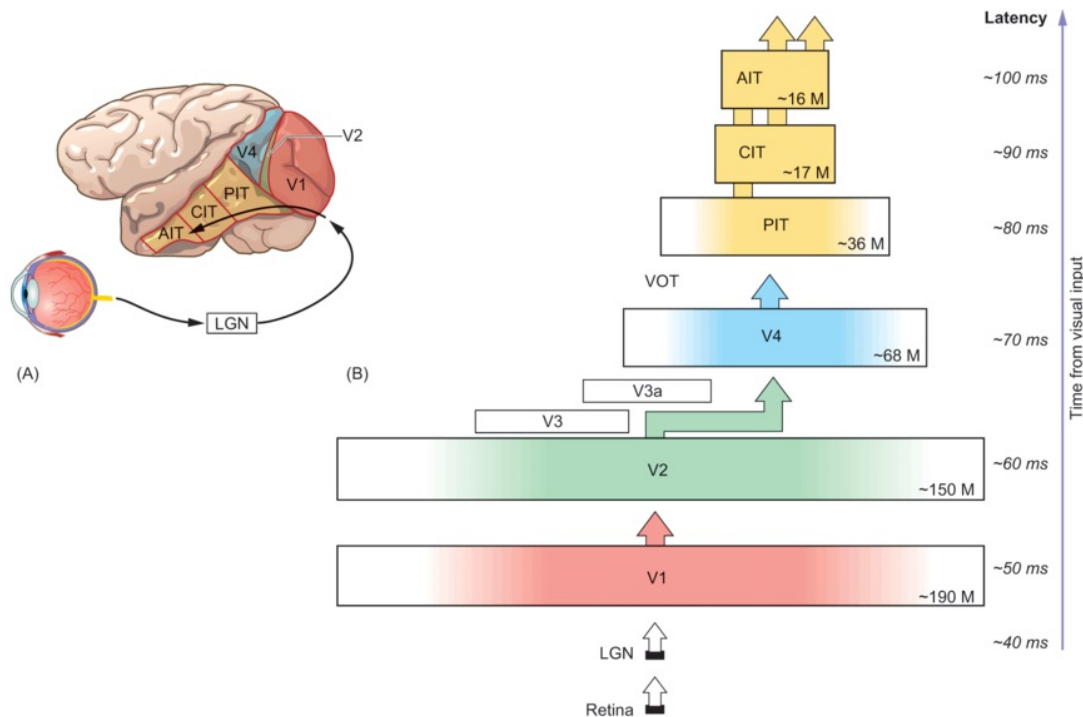


Figure 6.1 Ventral processing stream of the brain in the macaque.

(A) The ventral processing stream (shown here in yellow, on a lateral view of the left hemisphere) goes from V1 and extrastriate V2, V3, and V4, to the posterior, central, and anterior inferotemporal areas (PIT, CIT, and AIT, respectively). The right-hand panel (B) depicts the approximate number of neurons in each region (in millions) and lists the estimated latency of information arrival at each region in milliseconds (ms).

(from DiCarlo et al., [2012](#))

Certain characteristics of cells in inferotemporal areas seem to be especially adaptive for object recognition. As we move forward in the ventral stream, recording from individual cells along the stream, we can observe several important trends. The first trend is that cells in posterior regions fire to relatively simple stimuli, but cells further along the ventral stream fire to more complex and specific stimuli. So, whereas the areas just beyond primary visual cortex, such as V2, are likely to respond to one or more simple stimulus qualities (e.g., color, texture, length, width, orientation, direction of motion, spatial frequency), the cells in inferotemporal regions fire only in response to much more complex visual stimuli.

Decades ago, researchers discovered that cells in the inferotemporal cortex of monkeys exhibit maximal response to very specific forms, such as hands or faces (Gross et al., [1969](#), [1972](#); for review, see Gross, [2008](#)). The selectivity of these cells' responses was a serendipitous discovery. The researchers were having difficulty determining what type of stimulus would make cells in the inferotemporal region fire, and in frustration one of them moved a hand across the monkey's visual field. To the researchers' amazement, the cell fired more strongly than it had to any other object! They then tested other complex visual stimuli and found that in all cases the cell fired only in response to highly specific forms ([Figure 6.2](#)). These findings raised the possibility that complex objects may be coded for by small sets of individual cells that are specifically tuned to those objects.

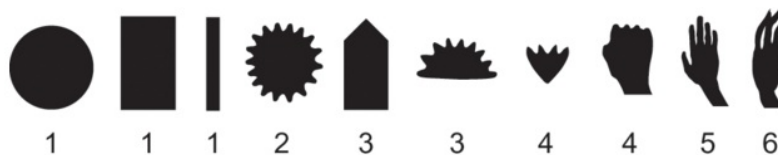
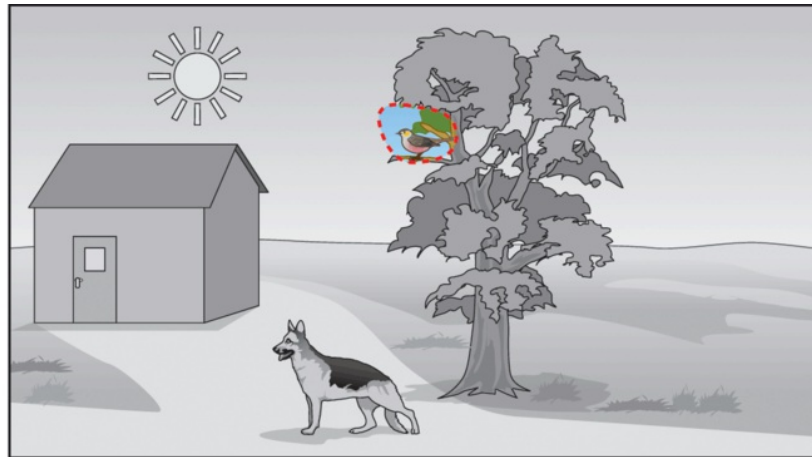


Figure 6.2 Examples of stimuli used to test the responsiveness of cells in the inferotemporal region of the macaque.

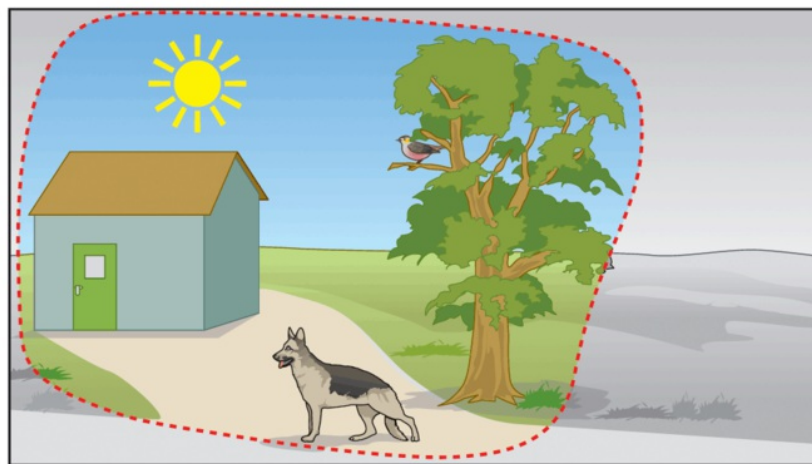
These stimuli are arranged from left to right in order of the degree to which they elicited a response, from 1 (no response) to 2 and 3 (little response) to 6 (maximal response). Note that the forms that make the cell fire are complicated and specific.

The second trend is that receptive fields become larger as we move further along the ventral stream (Wilson and Wilkinson, [2015](#)). As discussed in [Chapter 5](#), the [receptive field](#) of a cell is the area of visual space to which the cell is sensitive. Cells in primary visual cortex have very small receptive fields, whereas cells positioned further along the ventral visual processing stream respond to larger areas of space. [Figure 6.3](#) provides a schematic comparison of the relative sizes of the receptive fields for cells in posterior and anterior regions of the ventral visual stream. In primary visual cortex, cells that represent the foveal region may have receptive field sizes of less than 1 degree of visual angle. (Keep in mind that the entire visual field is approximately 180

degrees wide.) In contrast, receptive fields of individual cells in the monkey's inferotemporal cortex can range up to 26 degrees of visual angle (Op de Beeck and Vogels, [2000](#); for estimates in humans, see Dumoulin and Wandell, [2008](#); Yoshor et al., [2007](#)). The receptive fields of cells in the inferior temporal cortex almost always include the foveal, or central, region of processing (Desimone and Gross, [1979](#); Op de Beeck and Vogels, [2000](#)). In contrast to the peepholes of the primary visual cortex, which are distributed all over space, the receptive fields of the inferotemporal area can be considered analogous to a large picture window or glass wall that runs the length of one side of a house and always provides a view of what is directly in front.



(A)



(B)

Figure 6.3 Receptive field size of cells in primary visual cortex compared with that of cells in the inferotemporal region.

The receptive field is the region of space to which the cell is sensitive. If the optimal stimulus for an object falls outside its receptive field, the cell does not respond. In these pictures, the receptive field of a cell is indicated by a dashed circle. Areas within the receptive field are denoted in color, whereas those outside the receptive field are denoted in gray. (A) In primary visual cortex, the size of a cell's receptive field is small. (B) In contrast, the receptive field of a cell in the inferotemporal region is much larger, usually encompassing a wide expanse of visual space that always includes the midline.

A large receptive field is useful for object recognition because it can allow an object to be identified regardless of its size or where it is located in space. Consider

that when you look through a peephole, you see just a small portion of an object – a portion that is often too small to allow you to determine what you are viewing. Such is the problem with the small receptive field sizes of the primary visual cortex. However, as your field of view increases, so does your ability to detect whole objects, because the interrelationships among their parts can be appreciated. Thus, having a large receptive field allows the cell to respond to objects on the basis of their global shape, rather than just the size or location of local contours. A receptive field that includes the central region of visual space also aids object recognition. We typically direct our eyes so that an object we want to identify lands on the fovea or central region of the retina, where acuity is best.

Nevertheless, having a very large receptive field has a consequence: it means that some information about an item's position in space is lost. If a particular cell in the ventral stream responds to an object regardless of where in space it is located, it is impossible to tell where the object is located based on the firing of that cell. Cells in the ventral stream do preserve some spatial information, because their receptive fields are not nearly as wide as the entire visual field. However, spatial coding is not as precise in the ventral stream as in primary visual cortex. Luckily, the dorsal stream preserves spatial information, as we discuss in more detail in [Chapter 7](#).

Another attribute of cells in the ventral processing stream is that they are often sensitive to color (e.g., Edwards et al., [2003](#); Yasuda et al., [2010](#)). Color aids in object recognition because it allows us to separate an object from its background, a process often referred to as figure-ground separation. Consider an average street scene including parked cars, trees, buildings, and parking meters. Color may aid in quick identification of a car if it is yellow or white, a color distinct from the red brick building, the gray parking meter, the tan sidewalk, and the green trees that surround the car.

Given these properties of individual cells within the ventral stream, you may wonder how all the cells are organized within the cortical tissue. As you remember

from [Chapter 5](#), the primary visual cortex is exquisitely organized into columns, such that cells within a cortical column tend to respond best to the same line orientation and spatial location as one another. Do ventral stream areas have a kind of columnar structure as well? Structure within inferotemporal cortex is more difficult to discern than the structure of primary visual cortex. Because the preferred stimuli for cells in inferotemporal cortex are complex rather than simple features, it is unclear what set of images is best to use for testing cell preferences or finding what properties could be mapped systematically across the cortical surface.

Nevertheless, some evidence indicates a columnar structure in which nearby cells tend to respond best to similar properties. For example, researchers recorded the response of inferotemporal cortex cells to a set of 60–80 visual images, noting which cells respond best to which images, and found that neighboring cells tend to have somewhat similar response preferences (Kreiman et al., [2006](#); Tamura et al., [2005](#)). In addition, clusters of cells within the ventral stream appear to code for particular visual categories, such as faces or body parts (Grill-Spector and Weiner, [2014](#); Sato et al., [2013](#)). However, the organization of cells across inferotemporal cortex is still not fully understood.

To better understand the importance of the ventral stream in object recognition, we next turn to the study of deficits in recognition that occur following brain damage. Such deficits help to solidify the case that the ventral stream is crucial for object recognition, and they also raise important theoretical issues about object recognition that we will turn to in the second half of this chapter.

Deficits in Visual Object Recognition

The earliest evidence supporting the role of the ventral stream in object recognition came from neuropsychological patients with deficits in object recognition. These patients typically have damage that includes areas within the ventral stream of the cortex. [Visual agnosia](#) is an inability to recognize objects in the visual modality that

cannot be explained by other causes, such as an inability to do basic visual processing, a memory disorder, attentional problems, language difficulties, or general mental decline. Because the object can be recognized through other senses, the deficit is [modality specific](#), meaning that it manifests in only one of the senses.

For example, a woman with visual agnosia might be able to describe an object as a fuzzy brown, white, and black ovoid balanced on four short, stocky cylinders with a triangular-shaped appendage at one end and a very thin, very pointy, appendage, constantly in motion, at the other end. This description illustrates that her rudimentary visual abilities are intact. Furthermore, if this fuzzy ovoid nuzzled up to her so that she could feel its wet nose and whip-like tail, or if she heard its plaintive “boooooaaahhhhh, woaaaaaaahhh, woooooaaahhh” she would probably have little trouble identifying it as a dog, and possibly even as a beagle. Thus, although the woman cannot recognize the beagle in the visual modality, she can do so by the sense of touch or sound.

The word agnosia is Greek, meaning “without knowledge.” One of the most famous figures in psychology, Sigmund Freud – a man not traditionally known for his contributions to neuropsychology – first used this word to describe the neuropsychological disorder. He chose to call this syndrome agnosia because he argued that it was not the result of disruptions in sensory processes, but rather reflected an inability to gain access to previous knowledge or information about a sensory experience.

Apperceptive and Associative Agnosias

Traditionally, visual agnosias have been divided into two types: apperceptive and associative. This distinction dates to the 1890s and has been attributed to the German neurologist Lissauer (see Humphreys and Riddoch, [2014](#), for historical review). Lissauer suggested that [apperceptive agnosia](#) is a fundamental difficulty in forming a percept, a mental impression of something perceived by the senses. Although visual

information is processed in a rudimentary way (e.g., distinctions between light and dark can be made), the data cannot be bound together to allow the person to perceive a meaningful whole. In contrast, in [associative agnosia](#) basic visual information can be integrated to form a meaningful perceptual whole, yet that particular perceptual whole cannot be linked to stored knowledge. In other words, people with apperceptive agnosia in some sense have trouble “seeing” integrated objects, whereas people with associative agnosia can “see” objects but do not know what they are seeing (Farah, [2004](#); Humphreys and Riddoch, [2014](#)).

In apperceptive agnosia, rudimentary visual processing is intact at least to the degree that basic perceptual discriminations involving brightness, color, line orientation, and motion can be made. However, the person has lost the ability to coalesce this basic visual information into a percept, an entity, or a whole. People with apperceptive agnosia have little or no ability to discriminate between shapes, regardless of whether they are objects, faces, or letters, and they have no ability to copy or match simple shapes ([Figure 6.4](#)).

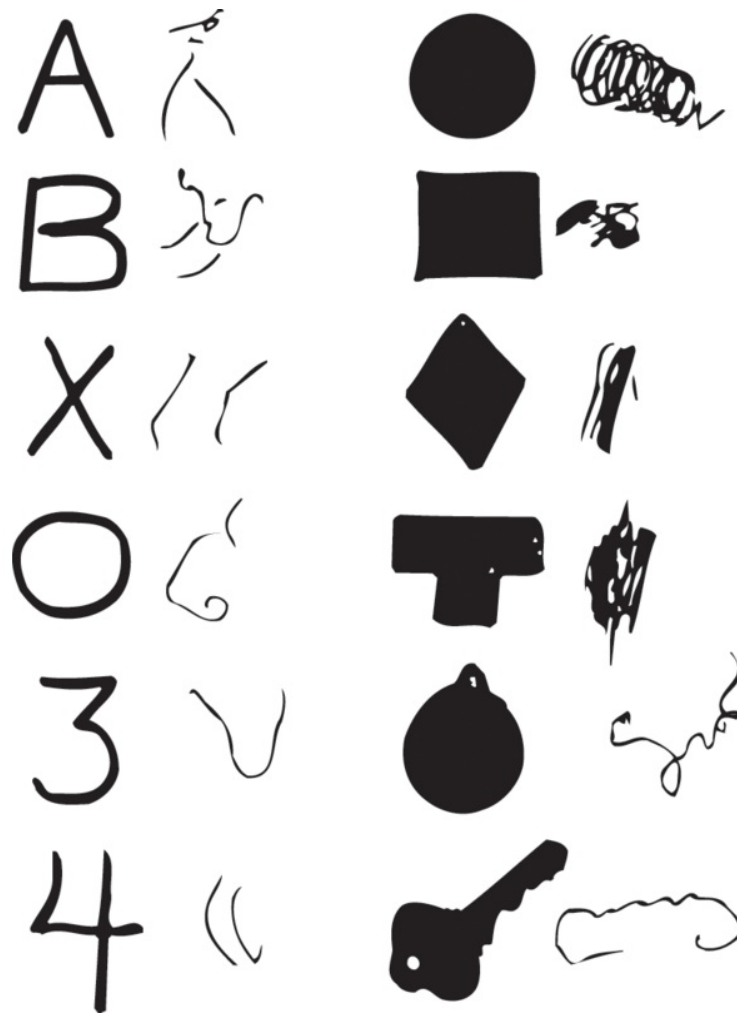


Figure 6.4 Example of the inability of a person with apperceptive agnosia to copy even the most basic forms.

The objects that the patient was asked to copy are on the left of each column, and the patient's attempts to do so are on the right.

These patients often perceive local features of an object correctly, but they suffer from an inability to group them together into the percept of a whole object. As an example of this deficit, look at [Figure 6.5](#). A person with apperceptive agnosia would not perceive the pattern as “this” because of the discontinuity between the parts of the “T” and the “H.” The person might read it as the number “7415,” because that ability relies on perceiving the simplest of visual features, line orientation.



Figure 6.5 Limited local form perception in an apperceptive agnosic patient.

The patient cannot read this visual pattern as the word “this” but rather reads it as “7415.”

In contrast, in associative agnosia, patients retain the ability to perform the perceptual grouping that persons with apperceptive agnosia find difficult. Copying a picture, such as the anchor shown in [Figure 6.6](#), is relatively easy for a patient with associative agnosia, even though the same task would be impossible for a person with apperceptive agnosia. However, a patient with associative agnosia would be unable to draw the same picture from memory. This difficulty does not arise from a general problem in memory; when asked, for example, what an anchor is, an individual with associative agnosia can provide a reasonable definition, such as “a brake for ships” (Ratcliff and Newcombe, [1982](#)). In some cases, people with associative agnosia are able to extract enough information from a visually presented item to determine its superordinate category (e.g., mammal, insect, or bird) but cannot correctly determine other attributes (e.g., whether it is tame or dangerous) (Warrington, [1975](#)).

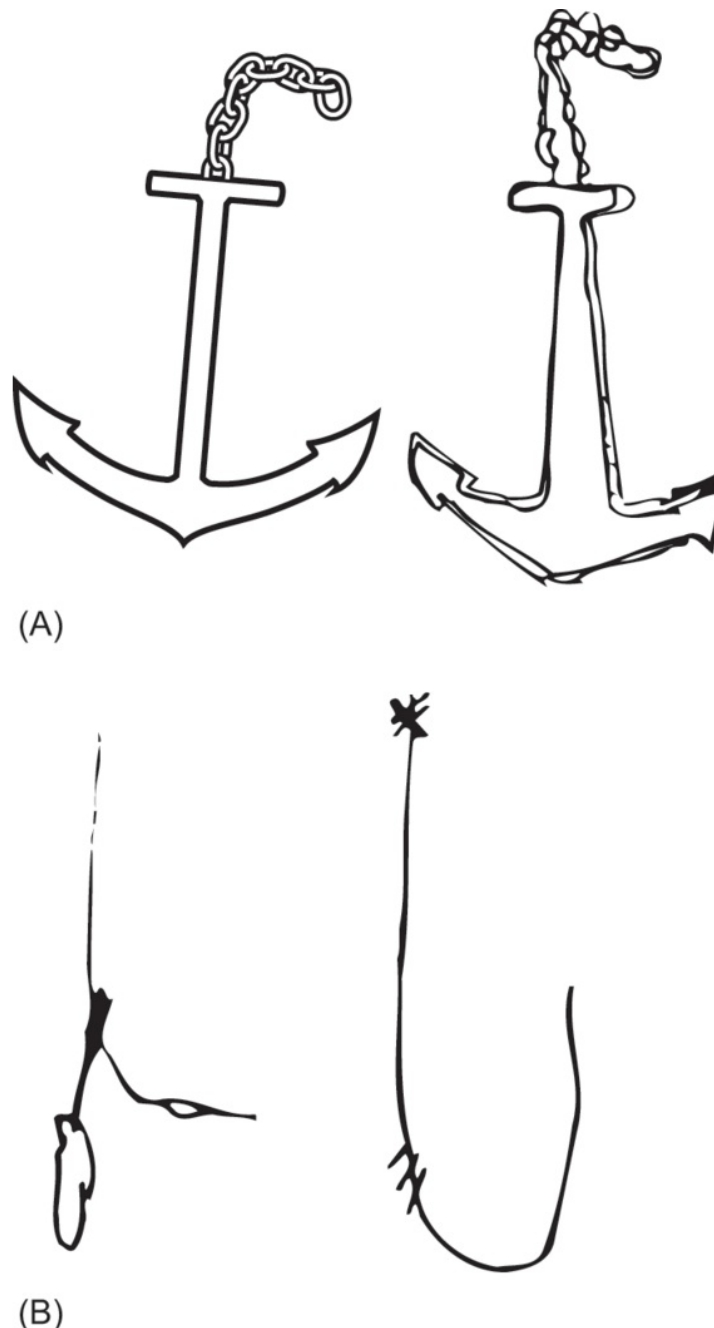


Figure 6.6 Drawing abilities of a person with associative agnosia.

(A) The patient's copy (right) of the model (left). Compared with the copying ability of a person with apperceptive agnosia (see [Figure 6.4](#)), this patient's ability to copy is much better. Yet, despite the patient's ability to copy the figure and assert that an anchor is "a brake for ships," he could identify neither the model nor his copy as an anchor. (B) The patient's attempts to respond to the request to draw an anchor. He was unable to retrieve the correct visual form from memory.

Because patients with this disorder can copy objects and can detect identical items from a set of similarly shaped objects, researchers originally presumed that their visual processing was intact – it was its linkage to semantic information in memory that was defective. Subsequent evidence, however, suggests that the perceptual abilities of these people, although better than those of patients with apperceptive agnosia, are not truly normal. First, although people with associative agnosia can perform matching and copying tasks, they use an exceedingly slow point-by-point or part-by-part comparison, which suggests that they are not obtaining a percept of the entire form. This strategy is different from that of neurologically intact individuals, who tend to draw the broad features first and then fill in the details.

Second, their deficits in object recognition become more severe as the input from a visual stimulus becomes more impoverished. They are best at recognizing real objects, next best with photographs, and worst with line drawings (which are most impoverished). Third, their errors are often ones of visual similarity, such as misidentifying a baseball bat as a paddle, knife, or thermometer, rather than as a bat. Finally, they have difficulty in matching objects that have no semantic associations, such as unfamiliar faces and complex novel shapes. If their visual processing were intact and the problem arose solely from a disconnection between visual form and semantics, they should have no trouble in matching these items (Farah, [2000](#); Devinsky et al., [2008](#)).

In summary, the main difference between apperceptive and associative agnosia lies in the type of visual information that can be processed. People with classic apperceptive agnosia can process crude visual information, such as color and line orientation, but lack the ability to derive the more complex visual information required to extract shape information, such as contour. In contrast, people with associative agnosia can perceive much more detailed information than those with apperceptive agnosia, as proven by their ability to match and copy items, and they can extract some information about general shape. However, subtle perceptual deficits in associative agnosia imply that it is probably too simplistic to posit, as Lissauer did, that associative agnosics have intact perception.

Given these differences in processing abilities between persons with apperceptive agnosia and associative agnosia, we would expect the site of brain damage to differ between these two populations, and indeed this is the case (see [Figure 6.7](#)). Patients with apperceptive agnosia usually have diffuse damage to the occipital lobe and surrounding areas, whereas the lesion site for associative agnosia varies but typically involves the occipitotemporal regions of both hemispheres and subadjacent white matter. Nonetheless, what is common to both syndromes is loss of the ability to link visual information to meaning.

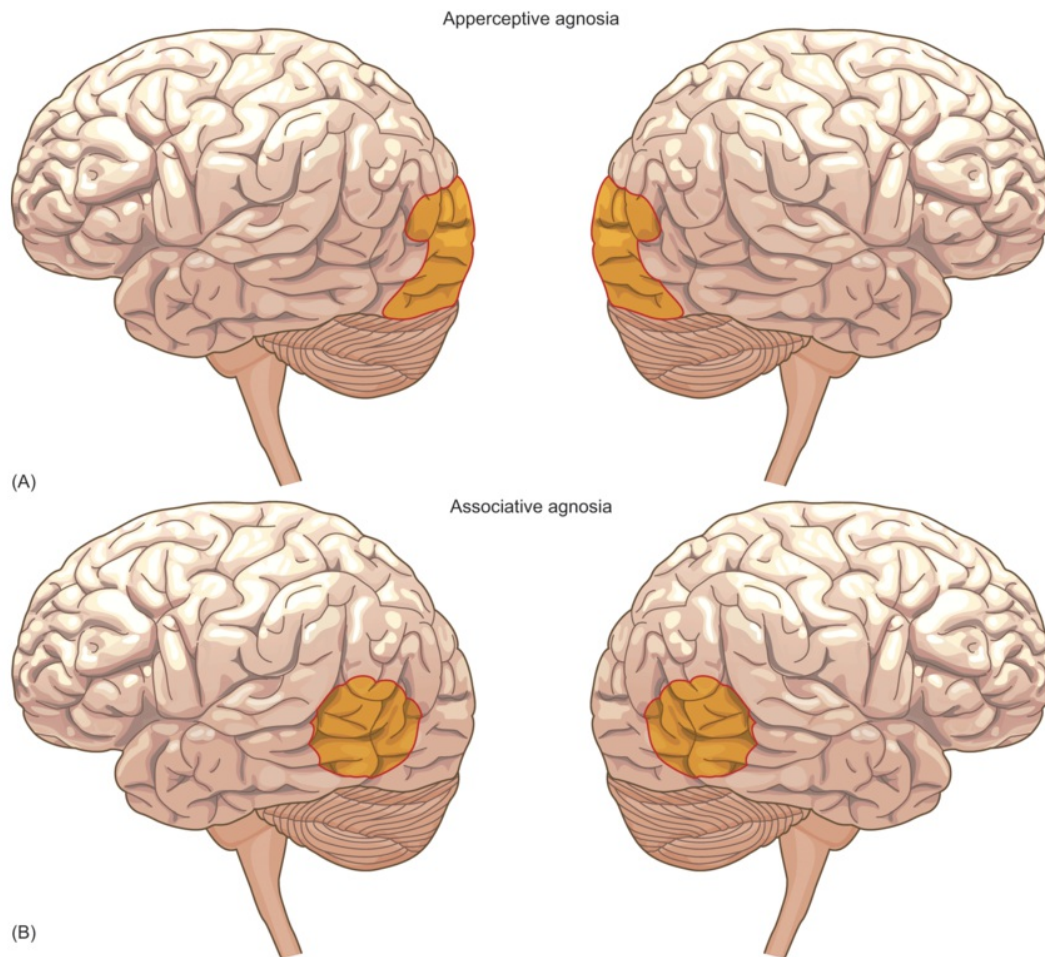


Figure 6.7 Regions of the brain typically damaged in apperceptive and associative agnosia.

(A) In apperceptive agnosia, damage occurs diffusely across occipital regions. (B) In associative agnosia, the damage tends to be bilateral at the occipitotemporal border. The typical lesion in associative agnosia is more anterior than the lesion in apperceptive agnosia.

Prosopagnosia: Agnosia for Faces

So far, we have discussed visual agnosia as a deficit in which the person loses the ability to recognize or identify all information in the visual modality. However, visual agnosia can be specific to a particular class of visual items. Probably the most widely studied is [prosopagnosia](#), which is a selective inability to recognize or differentiate among faces (Farah and Feinberg, [2006](#)). People with this disorder retain the ability to correctly identify other objects in the visual modality. Agnosias, however, can occur for

other visual forms. For example, there are patients who have specific difficulty in visually recognizing printed words, even though their other language abilities are normal and their abilities to recognize other visual objects are intact.

Studies of lesion locations suggest that prosopagnosia tends to occur with damage to the ventral stream of the right hemisphere, whereas visual agnosia for words tends to occur with damage to comparable regions of the left hemisphere, in a region known as the visual word form area (see [Figure 6.8](#); Martinaud et al., [2012](#)). These patterns fit with the idea that the right hemisphere is more involved in face perception and the left hemisphere is more involved in aspects of language, as we will discuss in greater detail later in this chapter and in [Chapter 8](#). Because prosopagnosia has been better studied than visual agnosia for words, we will focus on prosopagnosia here as an example of visual agnosia for a particular category of information.

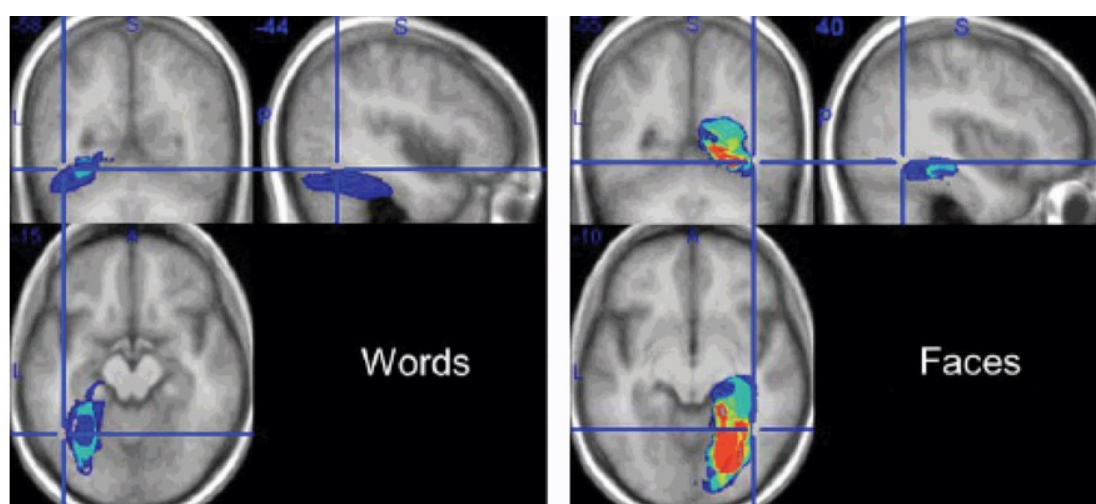


Figure 6.8 Damage to different brain areas disrupts word versus face recognition.

The left-hand panel illustrates lesion locations for patients with specific difficulties in recognizing visually presented words, and the right-hand panel illustrates lesions in patients with specific difficulties in recognizing faces (prosopagnosia).

(from Martinaud et al., [2012](#))

People with prosopagnosia typically can determine that a face is a face, which suggests that some aspects of high-level visual processing are intact. In some cases, prosopagnosics may be able to determine that a person's face depicts someone old or young, or male or female, and they may be able to identify the emotion that the face is expressing. Yet, they have lost the ability to recognize a particular face as belonging to an individual person. The impairment can be so severe that the patient with prosopagnosia may not be able to recognize her spouse, children, or even her own face!

Like other patients with agnosia, those with prosopagnosia do not have a general memory deficit. They can remember information about specific individuals and can recognize these people through other sensory modalities. Commonly, people with prosopagnosia attempt to compensate for their deficit by relying on distinctive visual nonfacial information, such as a person's hairstyle or a distinctive piece of clothing, or by relying on information in a nonvisual modality, such as voice or gait.

Traditionally, research focused on cases of prosopagnosia that were acquired due to neurological injury, meaning that the patient's performance was normal prior to brain damage. More recently, though, researchers have identified individuals who appear to be "face-blind" without any known brain trauma, a condition referred to as developmental (or congenital) prosopagnosia (Susilo and Duchaine, [2013](#)). Developmental prosopagnosia is thought to be present in approximately 2% of the general population. People with this condition report that they have had great difficulty recognizing faces for their entire lives, although they have no difficulty recognizing other visual objects. They have built up a lifetime's worth of compensatory strategies in order to recognize other people without having to rely on facial cues, instead relying on other cues such as voices or characteristic styles of movement.

Although these patients have no evident brain damage (unlike those with acquired prosopagnosia, who typically have had a stroke or other known head injury), we can infer that something must have gone awry in the development of face recognition mechanisms in the brain (Behrmann and Avidan, [2005](#); Towler and Eimer, [2012](#)).

Functional neuroimaging studies suggest that in people with developmental prosopagnosia compared to unimpaired people, anterior portions of the temporal lobe are not as highly activated by images of faces (Avidan et al., [2014](#); see also Lohse et al., [2016](#)). A genetic component likely contributes to developmental prosopagnosia, as the condition tends to run in families (Lee et al., [2010](#)).

One intriguing aspect of both acquired and developmental prosopagnosia is that in some cases these patients show evidence of some degree of face recognition even though they do not have conscious access to that information. Such evidence challenges the classic conception of agnosia, which assumes that agnosia results from a disruption in the ability to link perceptual patterns to information in memory. This implicit processing of faces has been demonstrated in two major ways: through physiological measurements and through behavioral priming studies.

Electrophysiological measures of neural activity provide evidence of some preserved face knowledge among prosopagnosics. For example, the P300 ERP response differed for familiar versus unfamiliar faces in one patient with acquired prosopagnosia (Bobes et al., [2004](#); see [Figure 6.9](#)). As you may remember, the P300 response is strongest to “oddball” stimuli presented within a sequence of similar stimuli. In this study, the prosopagnosic patient viewed a series of unfamiliar faces, with familiar faces interspersed as “oddballs” within the series. The P300 response was larger to the familiar faces, indicating that the patient’s brain was treating them as a category separate from the unfamiliar faces. Patients with developmental prosopagnosia also show evidence of implicit face knowledge in electrophysiological studies (e.g., Eimer et al., [2012](#)).

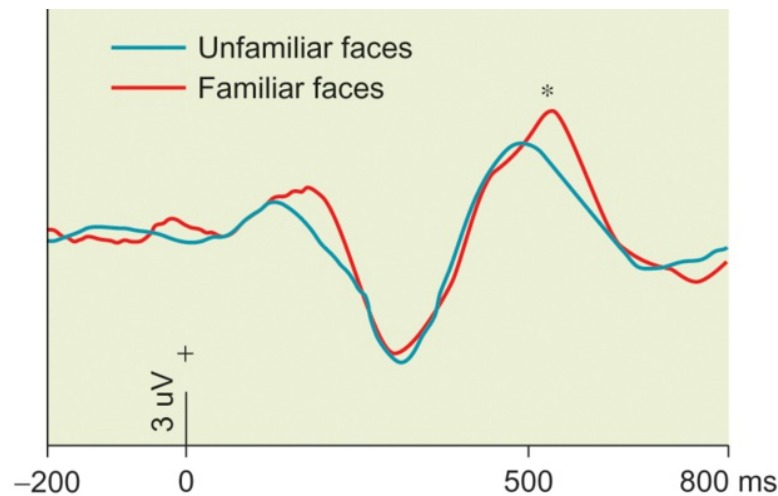


Figure 6.9 P300 response to familiar faces in a prosopagnosic patient.

Even though the patient does not have a memory of the previously familiar faces, the P300 event-related potential distinguishes between unfamiliar and familiar faces, suggesting that familiar faces are recognized implicitly at some level.

(from Bobes et al., [2004](#))

Other evidence for implicit recognition of faces in patients with prosopagnosia is the existence of interference effects that could occur only if the patient had some kind of access to information about facial identity. In one study, the task required a prosopagnosic patient to read a person's name aloud, and then classify the person by occupation (e.g., a musician or a politician). The name was positioned beside a face of someone from either a different occupation or the same occupation. Even though this prosopagnosic patient could neither identify the faces nor sort them according to occupation, the face nonetheless influenced performance in reading the name. Like neurologically intact adults, the patient took longer to read a person's name when it was situated next to the face of someone in a different occupation (De Haan et al., [1987](#)).

These studies suggest that some patients with prosopagnosia retain information about faces in memory, although it is not available in a way that allows for the explicit naming or categorizing of faces. These cases of prosopagnosia do not fit well with a model that presumes a total disconnection between the perceptual features of a face and its associated biographical information in memory. Perhaps these patients can only

encode a scant amount of visual information from a face. Alternatively, the threshold for recognizing a face may be greatly increased. This could preclude conscious access to the information under ordinary conditions, but still allow the low-level information that is processed to influence performance under certain conditions. We revisit the issue of implicit memory in more detail in [Chapter 9](#).

In sum, researchers are interested in the syndrome of prosopagnosia for a number of reasons. Studies of patients with prosopagnosia seem to indicate that faces are a special type of visual object, perhaps with a unique neural region dedicated to their processing. Further, prosopagnosia illustrates that the ability to identify an item as belonging to a specific category (e.g., determining that the visual pattern is a face) is distinct from the ability to remember the particulars about members within that category (e.g., determining that the face you are viewing is John's and not Tim's). In addition, implicit "recognition" in prosopagnosics raises interesting questions about how stored information is consciously retrieved. Later in the chapter, we will integrate evidence from prosopagnosia with evidence from other methodologies to address a range of theoretical questions about how the ventral stream regions support the visual recognition of objects.

Category-Specific Deficits in Object Recognition

So far we have discussed agnosia as a deficit in which the person loses the ability to recognize or identify information within a specific modality. However, in other cases a person has trouble identifying a certain category of objects even though the ability to recognize other categories of items in that same modality is undisturbed. For example, a person might have difficulty in identifying pictures of fruits and vegetables but not in identifying pictures of human-made objects. This disorder is known as a [category-specific deficit](#) (Caramazza and Mahon, [2003](#); Humphreys and Forde, [2001](#)).

Category-specific deficits differ from prosopagnosia (even though on the surface they both appear to involve particular categories of visual object) because category-specific deficits do not involve differentiating specific individuals within a category.

Rather, the deficit involves recognizing any object within the whole category. As we discussed above, a prosopagnosic can identify a face as a face, but cannot distinguish one person from another (e.g., José versus Julian). A patient with a category-specific deficit for fruit, for example, would have difficulty saying that an apple is an apple or an orange is an orange even though they may be able to tell that a bicycle is a bicycle.

Most category-specific deficits do not appear to be true agnosic deficits. Often, the deficits arise from difficulties within the semantic memory system (i.e., the system for meaning) rather than the visual system. For example, Warrington and Shallice ([1984](#)) found patients who could neither recognize pictures of a particular class of objects, nor provide an adequate definition of those items when told the names of the objects. Such findings suggest that these patients have lost access to memory for the affected class of items. We can contrast this with typical visual agnosia, in which a patient may not be able to recognize a picture of an object, let's say, a dog, but can still define what a dog is and can recognize it from its bark.

Although category-specific deficits may not be true visual agnosias, they still point to the role of visual information in semantic memory for certain kinds of objects. For example, some evidence suggests that visual information may be more important for recognizing living things (e.g., animals) compared to human-made artifacts (e.g., tools). When recognizing human-made objects such as crayons, hammers, and tables, we generally differentiate them according to function, or what actions we perform with them. However, this is not the case for living things, which typically don't perform functions for us. The best way to distinguish a leopard from a tiger is by visual features (the leopard has spots, whereas the tiger has stripes). According to this explanation, a more severe deficit might arise in recognizing animals than in identifying utensils, because the information in memory relies more heavily on the visual attributes of the item. This could account for some dissociations in which patients have more difficulty recognizing living things compared to nonliving things (Capitani et al., [2003](#); see also Thompson-Schill et al., [1999](#)).

Although they are generally not true visual agnosias, category-specific recognition

deficits continue to attract attention because they are so striking when observed in patients. From a scientific standpoint, the study of such deficits has the potential to help researchers better understand how different kinds of information about an object are stored in memory and contribute to recognition of the object.

Theoretical Issues in Visual Object Recognition

Evidence reviewed so far has told us that the ventral visual stream carries out visual object recognition, and that damage to this region can have profound effects on the ability to recognize objects in everyday life. However, there is much more to learn about how objects are actually represented in the neural tissue of the ventral stream. In the remaining sections, we focus on four interrelated questions that are being actively researched and debated in the cognitive neuroscience of visual object recognition.

First, how is a specific object represented within the visual stream: is a single object represented by the activity of only a few cells that are highly tuned for that particular kind of object, or is a larger swath of the neural tissue involved in representing any given object? Second, how does the ventral stream achieve perceptual invariance, which is the ability to recognize objects regardless of their orientation, position, or size? Third, is object perception based on understanding the individual parts of an object and then fitting those parts together, or is it based on a more holistic representation? Finally, we address the controversial issue of category specificity, the question of whether there are segments of the ventral stream that are dedicated to processing specific kinds of stimuli, such as faces.

Sparse Versus Population Coding for Objects

One basic question in object recognition is how individual cells in the ventral stream are involved in coding for the vast array of objects that a person (or monkey) is able to identify. What kind of code does the brain use? One way of thinking about this question is to ask whether the brain uses sparse coding or population coding (Reddy and

Kanwisher, 2006). By [sparse coding](#), we mean that a small but specific group of cells responds to the presence of a given object. Each object would excite a small set of cells, such that activity in that small set of cells would represent that particular object in our perception. According to a highly simplified version of this idea, cell #3 fires whenever an apple is present, whereas cell #9 fires whenever an orange is present (see [Figure 6.10A](#)).

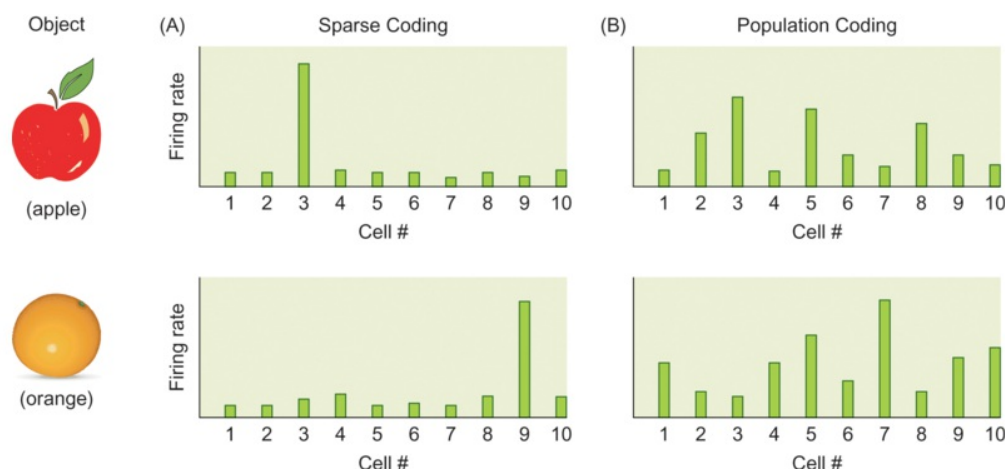


Figure 6.10 Schematic depiction of sparse versus population coding.

In sparse coding (A), a single cell (or small set) represents a specific object. For example, cell #3 codes for “apple” whereas cell #9 codes for “orange.” In population coding (B), different objects are coded by the pattern of activity across a population of cells, rather than by any individual cell.

The alternative point of view, [population coding](#), theorizes that the pattern of activity across a large population of cells codes for individual objects (see [Figure 6.10B](#)). According to the population coding viewpoint, the same cells participate in coding for different objects. For example, cells 1–10 might all be responsive to both apples and oranges, but the pattern of activity across these cells will differ in some way if the object is an apple rather than an orange.

To better distinguish these viewpoints, it is useful to think of the extreme positions. The extreme version of sparse coding is the [grandmother cell theory](#) (Barlow, 1985). According to this idea, there is a particular cell in the ventral processing stream whose

job is to fire when you see your grandmother. Some other cell fires when you see your grandfather, and another cell fires to your Uncle Bob, and so on. In many ways, this idea seems to be a logical extension of the trends we see in the visual stream: as we move forward within the stream, cells respond to more complex and specific stimuli because they take in more information from cells earlier in the ventral processing stream.

However, if you think about it logically, it doesn't make sense for the brain to have just one cell (or even a few) that identifies your grandmother. For starters, what happens when that particular cell dies? Do you suddenly become unable to recognize your grandmother, while still recognizing grandpa and Uncle Bob? It seems unlikely that the brain would have evolved a system in which representations could be so easily disrupted. Also, what happens when you learn to recognize a new object? Are there undedicated cells just waiting around to be assigned a new object to represent? That also seems unlikely. For these reasons, no one actually believes that the extreme version of the grandmother cell idea could be correct.

Let's also consider what an extreme population coding system might look like. Imagine that every cell in the ventral stream is involved in coding for every object. Each possible object would generate a unique pattern of activity across the millions of cells in the ventral stream. In [Chapter 4](#), we learned about a similar population coding scheme to code for planned actions in primary motor cortex (see page [111](#)). A population coding scheme would be more resilient than the grandmother cell system, because losing a couple of cells would not alter any given representation very much.

However, an extreme version of the population coding idea has other problems. Keep in mind that ultimately, the point of representing visual information is not just to represent it, but to be able to link that information with other information elsewhere in the brain. For example, you need to be able to link the sight of an apple with its taste, with its smell, with the word "apple," and with the action of biting an apple. If all the millions of cells in the ventral stream had to be involved in coding for the visual image of "apple," then all those cells would have to be somehow hooked up to cells in the

taste system, the smell system, the language system, and the motor control system. That is, there wouldn't be specific connections between "apple" cells in the ventral stream and "apple" cells in the taste or language areas, because all the ventral stream cells would be needed to code for the sight of an apple. Such a system would be pretty unwieldy.

As is often the case when extreme positions make little sense, the answer probably lies somewhere in-between. Representing "apple" probably involves more than one cell but less than all the cells in the ventral stream. Researchers are still trying to understand what point along the continuum between extreme sparse coding (grandmother cell idea) and extreme population coding (every cell codes for everything) best describes the way the ventral stream represents information.

Some evidence is broadly consistent with the population coding idea. For example, [Figure 6.11](#) illustrates the response of 61 different cells in monkey inferotemporal cortex as the monkey viewed two different images (top and bottom panel of the figure) (Lehky and Tanaka, [2016](#)). From this figure, you can see that the pattern of activity across the 61 cells distinguishes between the two images, rather than any one cell being the key to coding the presence of a particular image. This is consistent with population coding, rather than sparse coding.

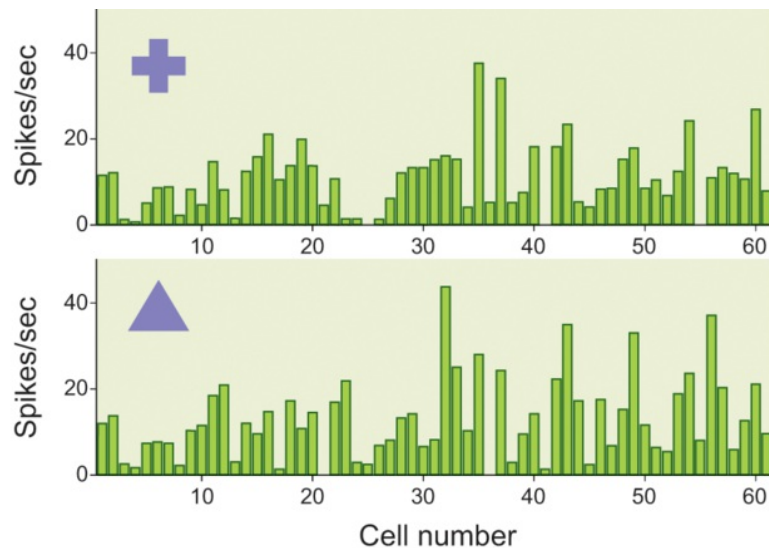


Figure 6.11 Population coding in monkey inferotemporal cortex.

Researchers recorded the response of 61 different cells to the two visual images shown in the insets. The pattern of activity across the population of cells distinguishes between the two images.

(from Lehy and Tanaka, [2016](#))

One of the difficulties in studying the issue of sparse versus population coding is the vast number of objects that people and other primates can recognize as well as the vast number (tens of thousands, if not millions) of cells in the inferotemporal cortex. Conclusions from a particular study are limited by the number of cells from which the researcher is recording as well as the particular set of objects that the researcher uses to test the cells. If a particular cell does not seem to “prefer” a particular object in the set, could it just be that the experimenter hasn’t yet found the right object to drive that cell’s response? Conversely, if a particular object does not seem to excite any one cell in particular, could it be that the experimenter isn’t recording from the right cell or set of cells?

These limitations have lessened somewhat as researchers have gained the technical ability to record from many cells at once in the primate brain, and as computational techniques have improved the ability to make sense of the patterns that emerge when recording from many cells during the viewing of large numbers of images. For example,

one group of researchers recorded from a few hundred randomly selected neurons in the inferotemporal lobe in monkeys, while presenting the monkeys with 77 different pictures of objects grouped into 8 categories, such as food, toys, monkey faces, and human faces (Hung et al., [2005](#)). The researchers fed the pattern of activity across the population of cells into a computer program, which was able to use the pattern of activity across the cells to correctly identify the category of each object as well as its specific identity. For example, based on the activity of 256 cells, the program could categorize the objects with 94% accuracy, and could correctly identify the specific object 72% of the time. Crucially, the researchers found that as more cells were added to the array, the ability to distinguish between different objects increased exponentially. This indicates that it is a pattern of activity across the whole set of cells, rather than the activity of object-specific “grandmother cells,” that most efficiently codes for object identity.

Taking another approach, other researchers have attempted to see whether changing activity in certain cells could change a monkey’s perception of a complex image. If so, this could suggest that those specific cells are crucial in representing a specific perception. In one study of this type, researchers demonstrated that stimulating face-preferring cells in a monkey’s inferotemporal cortex could make the monkey more likely to categorize an ambiguous picture as a face (Afraz et al., [2006](#); see also Afraz et al., [2015](#)). These findings indicate that activity in specific cells can contribute to causing or creating the perception of specific objects, although the findings don’t necessarily mean that these cells are the only ones critical in representing that object.

So far, most evidence seems to lean toward a population coding view, rather than a sparse coding view. However, some evidence from human epileptic patients once again raises the question of “grandmother cells.” Although most single-cell recording studies have been carried out with monkeys, on rare occasions single-cell recording is conducted with human epileptic patients. In some epileptic patients, recording electrodes are implanted to track the presence of abnormal electrical activity associated

with seizures. Researchers can take advantage of these situations by recording from those sites when different stimuli are presented (Rey et al., [2015](#)).

In a fascinating study of several patients, researchers found that individual cells had quite a high degree of specificity of response to certain objects (Quiroga et al., [2005](#)). One cell even had a strong preference for the face of the actress Jennifer Aniston, when seen from several different viewpoints, but did not respond to pictures of other actresses nor to pictures of Aniston together with actor Brad Pitt. Maybe this is not a “grandmother cell,” but is it the “Jennifer Aniston cell”?

Several factors complicate the interpretation of this study. First, as the researchers themselves point out, given the limited time that they tested the patient and given how many thousands of faces a person can recognize, it seems unlikely that they just happened upon the right actress who matched the cell where the electrode had been implanted. Rather, it seems more plausible that the tested cell probably responds to other faces too, but just not the others that were in their testing set.

A second complicating factor is that the cells in this study were located not in the inferotemporal cortex of the ventral stream, but instead in the hippocampus in the medial temporal lobe, where the electrodes had been implanted for seizure recording. For ethical reasons, the researchers couldn't just move the electrodes over to the ventral stream areas out of scientific curiosity. Therefore, while the study can tell us something about specificity of coding in the memory system, which the ventral stream feeds into, it doesn't tell us whether the ventral stream itself contains cells with such highly specific responses.

Indeed, continued study of these patients has found that some of the highly tuned cells in medial temporal cortex are multi-modal, seeming to represent a concept of a particular person, regardless of whether that person-concept is activated through visual or auditory means (Quiroga, [2012](#)). For example, one cell (shown in [Figure 6.12](#)) responded to pictures of the actor who plays the character Luke Skywalker in the Star Wars movies, and that same cell also responded to the visual presentation of the name

“Luke Skywalker” and to the auditory presentation of the name. The cell did not respond to other actors’ names or faces, although it did show some response to pictures of the Star Wars character Yoda, who is conceptually related to Luke Skywalker.

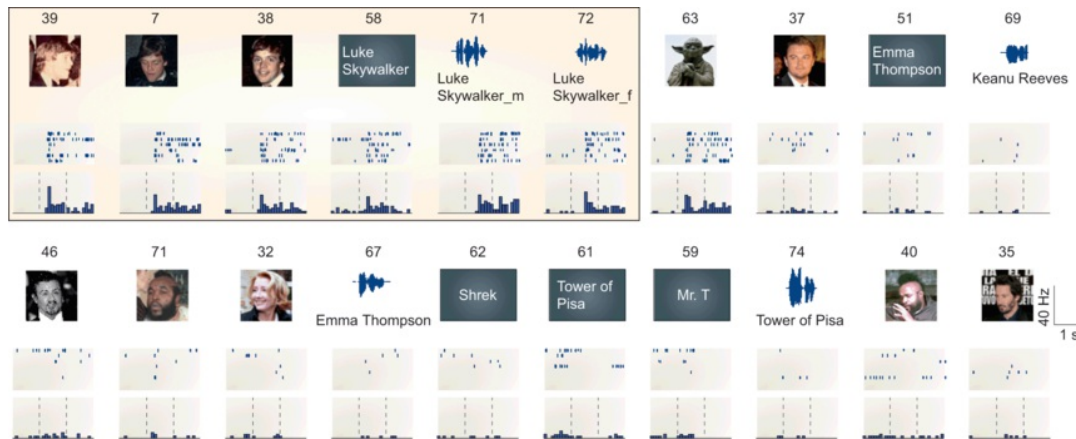


Figure 6.12 Responses of a single cell in a human epileptic patient to pictures of faces.

This cell in the medial temporal lobe responds preferentially to pictures of the actor who plays the character Luke Skywalker in the Star Wars movies, as well as responding to visual and auditory (read by male or female voice) presentations of the name “Luke Skywalker”.

(from Quiroga, [2012](#))

As noted above, these studies of human epileptic patients do not tell us directly about ventral stream properties because the cells in these studies were in the medial rather than the lateral ventral temporal lobe. The “Jennifer Aniston/Luke Skywalker” studies, however, do give an example of what sparse coding might look like. In addition, they remind us that object recognition does not end in the ventral stream. Ventral stream areas communicate information about visual objects to the medial temporal lobe, which, as we will learn in [Chapter 9](#), plays an important role in associative memories across sensory modalities.

The Problem of Invariance in Recognition

An amazing aspect of our visual recognition is the ability to identify objects under myriad conditions. For example, you can easily recognize an apple regardless of whether it is depicted as the logo on a computer, seen in a bowl of fruit in front of you, or depicted in a painting. This is known as form-cue invariance, because the brain's categorization is constant regardless of the form of the cue that represents that object. People are also easily able to recognize objects seen from different angles, at different positions or sizes, and under different kinds of illumination, a phenomenon known as perceptual constancy. The ability to recognize objects across so many varying conditions implies that at some level, our mental representation of objects is fairly abstract, in the sense of being removed from or independent of the original stimulus conditions (DiCarlo et al., [2012](#)).

How can we tell if a particular brain region supports such abstract representations of objects? One neuroimaging method that is especially useful is the adaptation method (Krekelberg et al., [2006](#)). The adaptation method takes advantage of the fact that the brain's response to an item decreases (adapts) with repeated viewing of the item. In a typical adaptation study, participants first view a particular item for some period of time to become adapted to it, and brain activity decreases correspondingly (see [Figure 6.13](#)). If the same item is then presented again, brain activity remains at a low level, because the neurons within that region that code for the item are adapted to its presence. If a new object is presented, however, brain activity increases. The idea is that neurons within that brain region that code for the new object have not been adapted, and therefore they show a strong response to the new object.

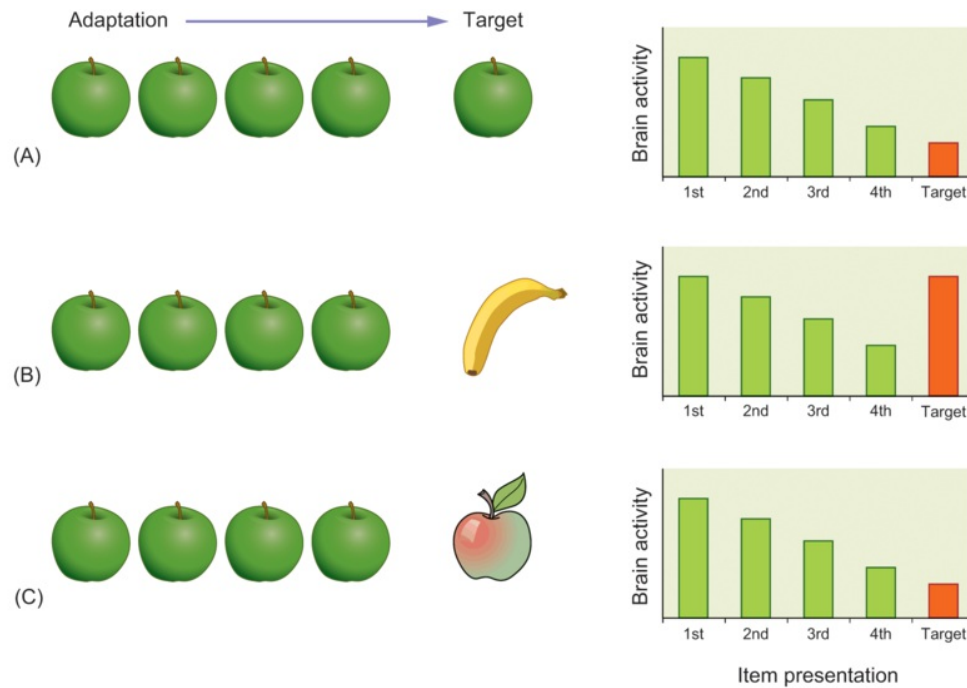


Figure 6.13 The logic of the fMRI adaptation method.

Participants are adapted to a particular visual image, and then either the same image is shown again as the target (row A) or a different image is shown as the target (row B). Brain activity decreases, or adapts, to the repeated image, but it increases again (recovers from adaptation) with the presentation of the new item. To test whether a brain region shows form-cue invariance, researchers present a target that is the same object as the adapted item, but in a different visual form (such as a line drawing versus a photograph). If adaptation persists, as shown in row C, the brain region is treating the adapted item and target item as similar, and therefore is showing form-cue invariance.

Now, consider how this method can be used to test whether a brain region shows form-cue invariance. Logically, if a portion of the brain exhibits invariance, it should show just as much of an adaptation effect when presented with two different instances of the same object (e.g., line drawing of an apple and photograph of an apple) as when presented with two identical representations of the object. In other words, if a brain region continues to show adaptation to a new depiction of the same type of object, the brain region is treating that new depiction just like the old version to which it was already adapted, and therefore it is showing evidence of form-cue invariance.

Neuroimaging studies using the adaptation method have shown that a particular region within the ventral stream seems to display perceptual constancy and form-cue invariance. This region, the lateral occipital complex (LOC) (see [Figure 6.14](#)), is located at the section of the ventral stream just beyond (anterior to) the retinotopically mapped extrastriate areas such as V2 and V4. The LOC is more responsive to shapes than to textures, and it shows evidence of perceptual constancy across variations in size and location of the shape (Kanwisher and Dilks, [2014](#)). In addition, activation in the LOC exhibits a similar response to both line drawings and photographs of the same object, indicating form-cue invariance. Unlike other regions further along the ventral stream that we will discuss later, the LOC does not appear to be selective for particular categories of objects (such as faces, bodies, or words), but rather responds to many different kinds of visual objects. Together these characteristics suggest that the LOC represents a stage in visual processing in which retinotopic representations are transformed into relatively abstract shape representations that support recognition across variation in size, precise form, and location.

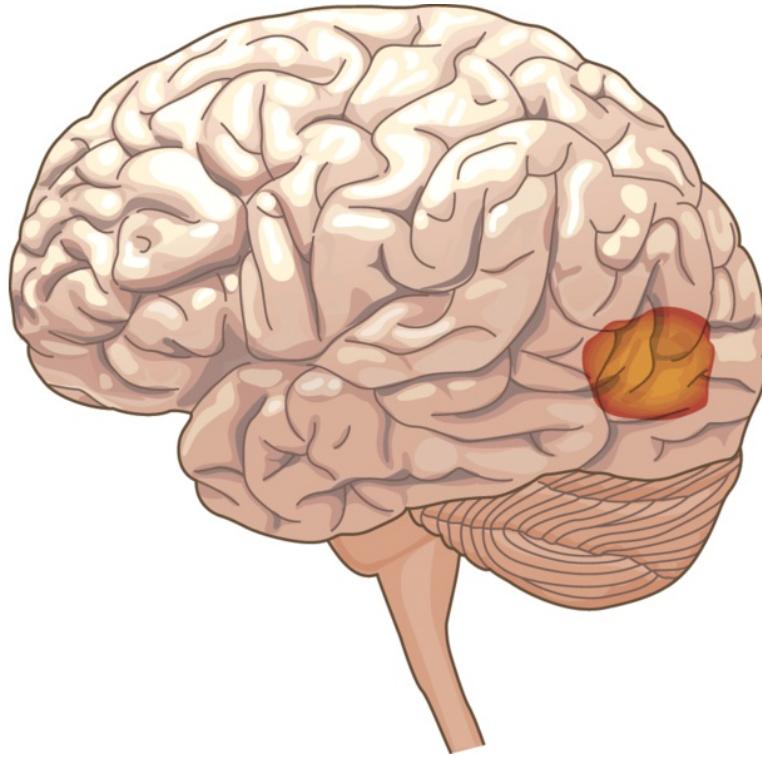


Figure 6.14 The location of the lateral occipital complex.

This region responds to visual shapes, and its response is fairly consistent across variations in size, position, and precise form of the object.

(e.g., photo versus line drawing)

Some research has focused specifically on the problem of position (or location) invariance, which refers to our ability to recognize an object regardless of where it appears in the visual field. Despite the fact this ability is easily evident in our everyday lives, researchers are still puzzling over how the visual system is able to achieve such invariance. As we've already discussed, ventral stream cells have larger receptive fields than primary visual cortex cells, which allows the ventral stream cells to respond to an object across a broader area of space than would be possible based on primary visual cortex cells alone. But at the same time, research has shown that individual cells within the ventral stream tend to have preferred spatial locations; that is, their responses to complex visual forms can be affected by small changes in the spatial location of the form (e.g., DiCarlo and Maunsell, [2003](#)). Other research has shown that when monkeys are trained to recognize a novel object in a particular spatial location on the retina, cells

within the inferotemporal cortex later respond best to that form at that location, as opposed to other locations on the retina (Cox and DiCarlo, [2008](#)). In ways that are not fully understood, position-invariant recognition arises from ventral stream cells that have position preferences.

Additional research has focused specifically on the vexing problem of viewpoint invariance. Our everyday experience in recognizing objects can tell us two things about the question of viewpoint invariance. First, we can easily recognize objects from multiple viewpoints. That is, you can recognize your dog Spot regardless of whether you see him from the side, face on, or from behind. Despite all those viewpoints, you know it is still Spot. At the same time, though, your brain also notices viewpoints. For example, you can easily tell the difference between a view of Spot when you see him from behind (such as when you are walking him) and a view of Spot from the front (such as when he is running up to you to get a treat). So, your representation of objects is flexible enough that you can easily tell the viewpoint from which you're seeing Spot, as well as realizing that it is still Spot no matter which way you look at him.

Scientists who study object recognition have long been concerned with whether neural representations of objects are primarily viewpoint-independent or viewpoint-dependent (Peissig and Tarr, [2007](#)). That is, do neural representations of an object depend on the viewpoint from which the object is seen? This debate centers around the issue of how the brain takes the two-dimensional information from the retina and creates a three-dimensional representation of an object so that it can be recognized from any viewpoint.

One classic explanation assumes that the brain actually creates a viewpoint-independent three-dimensional representation of an object that is built up from two-dimensional information. For example, it may be that the brain first extracts viewpoint-specific information, and then uses that representation to build a more abstract three-dimensional representation that is independent of viewpoint. A computational model that posited this basic idea was proposed by computer scientist David Marr ([1982](#)). According to Marr, extraction of a full three-dimensional image happens in several

stages. First, the visual system constructs a [primal sketch](#) of features in the visual world, which segments dark from light regions and groups them together via gestalt principles. From information in that primal sketch, the system deduces the relative depth of different surfaces and edges, and constructs a representation of what parts of an object are in front or behind. Finally, the system develops a full [three-dimensional \(3-D\) representation](#) of that object that is not specific to a viewpoint, but is more abstract and viewpoint-independent.

Other researchers argue that recognition of objects from multiple viewpoints does not depend on having a full 3-D viewpoint-independent representation of the object, but rather depends on some kind of systematic integration or interpolation across a set of [viewer-centered representations](#) (see Tarr and Bülthoff, [1998](#), for a review). For example, starting with a representation of the image from a viewer-specific vantage point, the system may make a guess about what an object might be, compare that to stored representations of objects, measure the difference, and generate another hypothesis if the match is too poor. Notice that in these types of models, recognition of an object from a particular viewpoint depends heavily on comparison with stored descriptions in the brain (Riesenhuber and Poggio, [2000](#)).

Several different kinds of evidence support some degree of viewpoint dependency in recognition. For example, behavioral studies demonstrate that although people are pretty good at recognizing objects from multiple viewpoints, their recognition tends to be faster and more accurate when they see the object from its most typical viewpoint, or the viewpoint that they have seen most often (e.g., Hayward and Tarr, [1997](#)). In addition, using the adaptation technique described above, researchers found that activity in the LOC does not exhibit invariance for an object's viewpoint until the ages of 5–10, in contrast to size invariance, which occurs at much younger ages (Nishimura et al., [2015](#)).

Research with monkeys has also found that during learning of new objects, cells became tuned to specific viewpoints of those objects. In one study, monkeys were presented with novel objects seen from specific viewpoints (Logothetis and Pauls,

[1995](#); see also Murty and Arun, [2015](#)). After training, monkeys saw those same objects in both the trained and untrained viewpoints. Recognition performance was best for the trained viewpoints and for views within about 40 degrees of rotation from the trained viewpoints. Nonetheless, monkeys could also interpolate to recognize the objects when presented with views that fell in-between the viewpoints on which they had been trained. Further, individual cells in the ventral stream responded best to the objects presented in the trained viewpoints. These results suggest that cells become tuned to certain two-dimensional views of an object through experience, and that such viewpoint-specific cells may support some degree of recognition of alternative viewpoints.

Single-cell recording studies indicate that the brain uses both viewpoint-independent and viewpoint-dependent codes in different subsets of cells. Some ventral stream cells respond to a favored object in a way that remains unchanged regardless of the viewpoint, whereas other cells' responses to an object change quite a lot depending on the orientation of the object. For example, one study in monkeys identified groups of cells with different viewpoint-dependencies in response to preferred faces (see [Figure 6.15](#); Freiwald and Tsao, [2010](#)). One group of cells tended to respond only to the preferred face in a specific orientation, another group of cells tended to respond best to a face in a particular orientation as well as its mirror-image, and a third group of cells tended to respond similarly to a preferred face regardless of orientation. Neuroimaging studies in humans have also found a progression along the ventral stream from viewpoint-dependence at earlier stages to viewpoint-invariance at later stages (Axelrod and Yovel, [2012](#)).

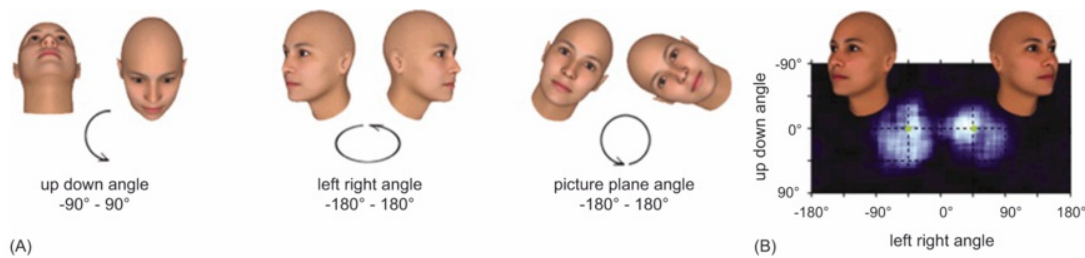


Figure 6.15 Example of viewpoint-dependency in coding by ventral stream cells.

Panel A depicts sample images shown to monkeys while recordings were taken from patches of cells in the inferotemporal cortex. Faces differed in their orientation in the up-down plane, left-right angle, and picture plane. Panel B depicts the response of an individual cell that shows a preference for a particular orientation as well as its mirror-image. Bright colors indicate a stronger response of the cell. Other cells (not shown) showed no preference for orientation, responding similarly to preferred faces regardless of orientation.

(from Freiwald and Tsao, [2010](#))

In sum, researchers are still trying to decode how the brain achieves the ability to recognize objects in an abstract way that does not depend on the particulars of how the image of that object falls on the retina. As the visual image is processed throughout the ventral stream, going from primary visual cortex to inferotemporal cortex, the image is re-represented in ways that become more abstracted from the actual retinal image, thus allowing complex objects to be differentiated and recognized (DiCarlo and Cox, [2007](#); DiCarlo et al., [2012](#)). Determining the precise mechanisms by which this happens will not only help solve the code of object recognition in the brain, but will help engineers in designing computer-based object-recognition systems (Poggio and Ullman, [2013](#)).

Feature-Based Versus Configural Coding of Objects

Although we recognize an object as one integrated entity, most objects are composed of parts. For example, a hand is composed of fingers, a thumb, and a palm; a cup is composed of a handle and a cylinder; and a car is composed of wheels, body, doors, and windows. To what extent is our recognition of objects influenced by the features of

individual parts, and to what extent is our recognition of objects dependent on the way those parts fit together in certain configurations to make a whole?

Clearly, integrating parts into whole objects is an important function of the visual system. As you remember from earlier in the chapter, apperceptive agnosics are unable to integrate parts into wholes, and this radically changes their experience of visual objects. For example, a case study presented one agnosic patient with novel objects composed of two parts. The patient was able to tell correctly when one of the parts was replaced by a new part, but was unable to tell when the same two parts were presented together but in a different configuration (Behrmann et al., [2006](#)). This evidence indicates that the integration of parts into wholes requires additional processing beyond that of recognizing individual parts.

What is the relative importance of features versus configural information in object recognition? In other words, do we tend to rely more on individual features or on the way those features are put together when we attempt to identify an object? One answer is that features and configural information matter differently to the two hemispheres. Lesions to the temporal lobe of the left hemisphere disrupt the ability to perceive local features, but not global (holistic) aspects of an item, whereas lesions of the right hemisphere have the opposite effect, disrupting the ability to perceive global, but not local, aspects of form (see [Figure 6.16](#); Robertson et al., [1988](#)). Thus, there appear to be two distinct neural mechanisms involved in object recognition: one lateralized to the left ventral stream, important for analyzing the parts of objects; and another lateralized to the right ventral stream, important for analyzing whole forms.

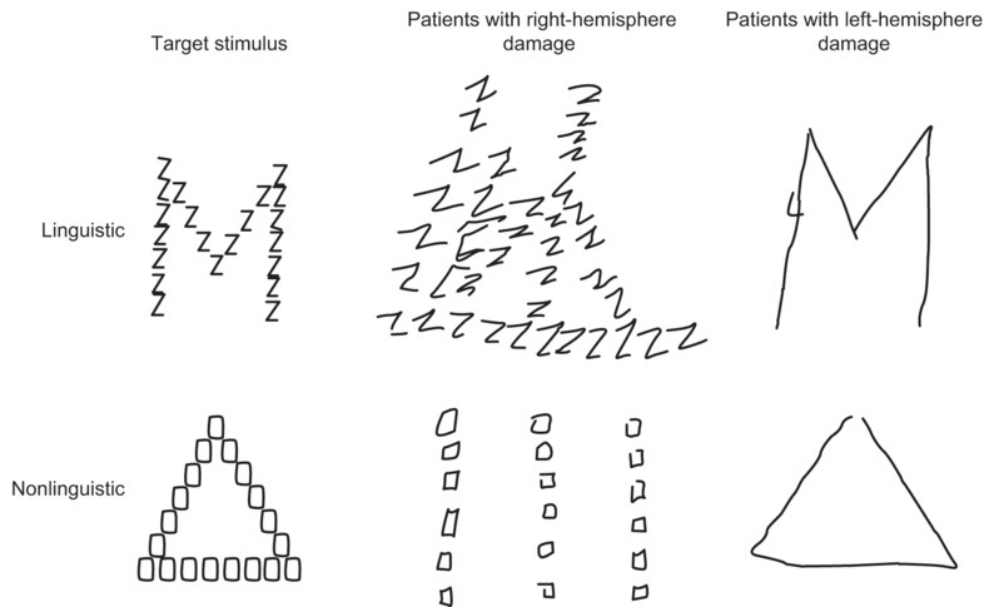


Figure 6.16 Hemispheric differences between global and local processing.

Patients who sustain damage to the right hemisphere can correctly draw the local, or component, parts of objects, as illustrated by the correct drawings of the Zs and the rectangles. However, for the right-hemisphere damaged patient, the global form is incorrect. In contrast, patients who sustain damage to the left hemisphere can correctly draw the global form of the items but not the local component parts.

Researchers have also discovered that configural information – that is, the overall relationship between different parts of an item – is especially important for object categories for which we have a lot of expertise. This is probably best illustrated by studies on face recognition examining what is known as the [inversion effect](#) (Yin, 1970). The basic logic is that if configural information is especially important for recognizing certain objects, then recognition ought to be substantially poorer when the objects are turned upside down (inverted), because inversion specifically disrupts configural relationships while leaving the parts intact. Indeed, inversion especially impairs the recognition of faces compared to other objects, such as houses and cars, suggesting that configural information is key for face recognition (Rhodes and Calder, 2014). [Figure 6.17](#) illustrates another way in which inverted stimuli can disrupt configural processing.

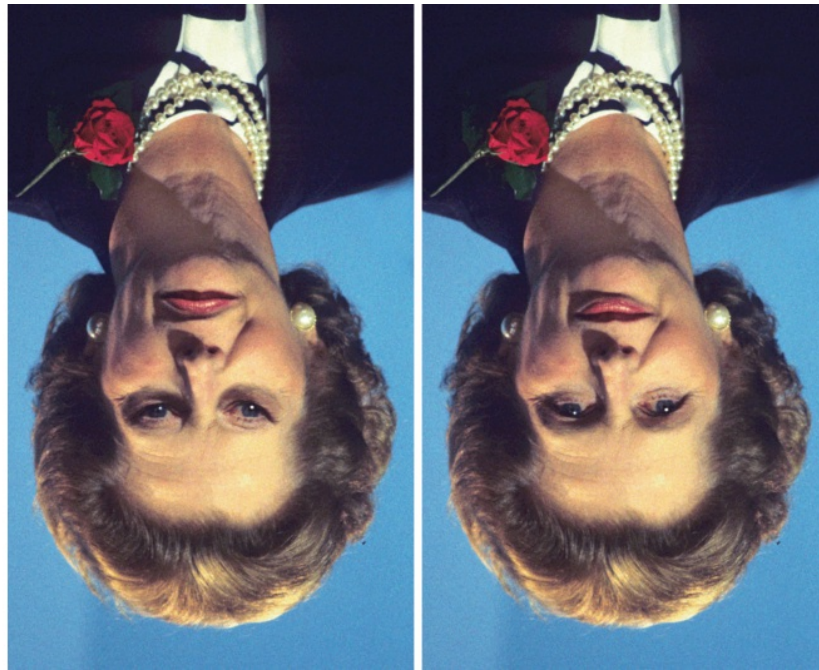


Figure 6.17 Example of the importance of configural information for recognizing faces.

Examine the two faces and notice how from this vantage point they look similar. Now view the figure upside down so that the two faces are right-side up. You should immediately see a difference. This exercise, called the Thompson illusion, demonstrates the degree to which configural strategies are important for the processing of faces in the upright orientation and how they are minimized when the faces are inverted.

Source: David Cole / Alamy Stock Photo

Configural processing deficits appear to contribute to the severe face recognition difficulties of at least some prosopagnosic patients. For example, researchers reported on one patient with acquired prosopagnosia who had great difficulty in recognizing faces in their upright position, but performed similarly to control participants in recognizing upside-down faces (Jansari et al., [2015](#)). The patient could also recognize familiar faces as quickly as did control participants when they were presented in a fragmented form that disrupted the global configuration but left individual features intact. Interestingly, the patient also had difficulty identifying the global shape in

composite figures such as those shown in [Figure 6.16](#). Because otherwise the patient's recognition of familiar objects was normal, the researchers surmised that he was able to use local features to recognize most objects, as well as upside-down or fragmented faces. However, whereas normal control participants rely upon global, configural information for recognizing upright faces, the patient was unable to do so, disrupting performance significantly for this kind of visual object.

Although inversion effects – the typical disruption in performance when stimuli are turned upside down – are especially notable for faces, other stimuli for which people have expertise can also show inversion effects. For example, one group of investigators compared how well college students and judges of show dogs could distinguish between pictures of different dogs (Diamond and Carey, [1986](#)). As expected, the college students exhibited a much smaller inversion effect for pictures of show dogs than for faces. In other words, they had more trouble recognizing the faces when upside-down versus rightside-up, but this effect was not as pronounced with the dog pictures. In contrast, the show-dog judges displayed as large an inversion effect for show dogs as for faces, indicating that configural information processing played an important role in the experienced judges' identification of dogs (though see Robbins and McKone, [2007](#)). Another study found inversion effects for fingerprints in people who were experts at recognizing fingerprint patterns (Busey and Vanderkolk, [2005](#)).

Other studies have found that face-inversion effects are most pronounced for same-race faces, with which participants typically have more experience. For example, Chinese people exhibit a greater inversion effect for Chinese than Caucasian faces, whereas Caucasian people exhibit the opposite pattern (Rhodes et al., [1989](#)). These results probably occur because we have more experience with the configural nature of the faces of individuals of our own race than with that of other races. When asked to differentiate among faces, we can do so more easily if they fit into a configuration with which we are familiar.

How exactly are individual features combined into whole shapes? Researchers have distinguished between two possible models. One model, referred to as conjunctive encoding, assumes that features are explicitly conjoined, or linked together, through hierarchical processing in which lower-level regions representing features send their output to higher-level regions representing the shapes that result from the joining of those features. An alternative model, referred to as nonlocal binding, assumes that a whole object is represented simply by the co-activation of units that represent the parts of the object in particular locations. Under this alternative model, there is no separate unit or region that represents the whole, but rather the whole is perceived when the units representing all the constituent parts are simultaneously activated.

Although the value of these two models is still being debated, evidence tends to support the conjunctive coding model. For example, studies in monkeys have found evidence of clusters of cells in inferotemporal cortex that respond best to specific combinations of features. In one study, researchers used optical imaging to identify regions of the cortex in the macaque monkey that were activated in response to configurations of features, such as a 2-D drawing of a cat, but were not responsive to individual elements of that drawing, such as just the cat's head or just the cat's body (see [Figure 6.18A](#); Yamane et al., [2006](#)). The researchers then recorded from individual cells within these identified areas of cortex, and found cells that responded best when features of an object were arranged in a particular spatial configuration ([Figure 6.18B](#)). These results indicate that individual cells can code for combinations of features in particular spatial configurations.

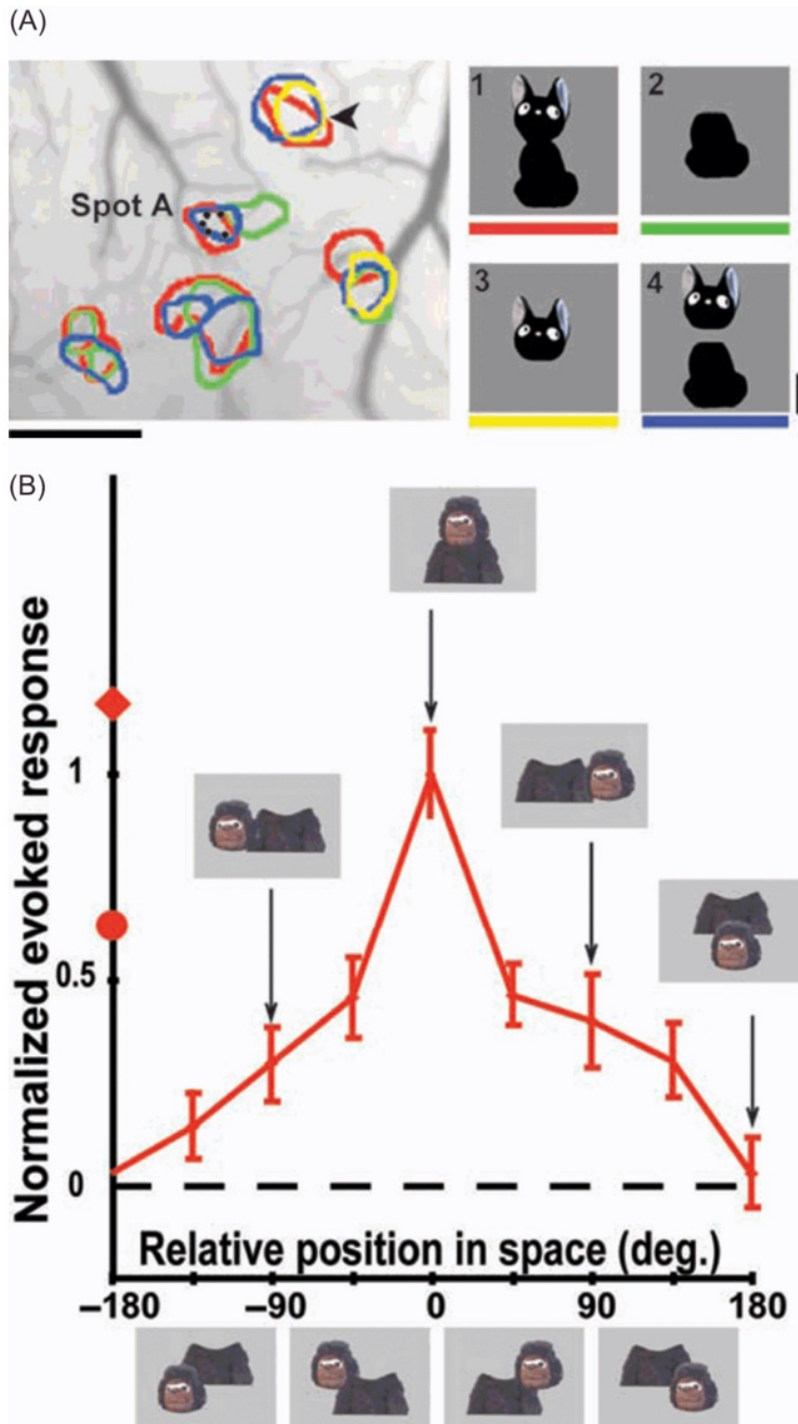


Figure 6.18 Cells in inferotemporal cortex that prefer configurations of parts.

(A) Results from an optical imaging study in monkeys that examined activity measured at the cortical surface in response to object parts and their configurations. Colored circles indicate the region of the brain that is responsive to the stimuli shown on the right (1-red; 2-green; 3-yellow, 4-blue). Area A showed activity only in response to the cat head and body together (stimuli 1 and 4). In contrast, the area

indicated by the arrow was responsive to all cat heads (stimuli 1, 3, and 4), regardless of whether they occurred with bodies or not. (B) In the same study, researchers measured spike rates of individual neurons in brain areas such as Area A from part A of the figure. Individual neurons tended to have a preference for object parts arranged in a particular configuration.

Source: Figures 4A and 6A from Yamane, Y., et al. (2006). Representation of the spatial relationship among object parts by neurons in macaque inferotemporal cortex. *Journal of Neurophysiology*, 96, 3147–3156. Reprinted by permission of American Physiological Society. *J Neurophysiol* 96: 3147–3156, 2006. Yukako Yamane, Kazushige Tsunoda, Madoka Matsumoto, Adam N. Phillips, and Manabu Tanifuji.

Another study found that when monkeys were trained to recognize novel two-part objects, cells in the inferotemporal cortex fired more vigorously when both features were present compared with what would be expected from the presence of either feature alone (Baker et al., 2002). In other words, as the monkey learned to recognize these novel objects, cells in the inferotemporal cortex became especially sensitive to the conjunction of the two features that were part of the object. This cellular-level evidence suggests a possible mechanism for the shift from featural to configural encoding as we become more experienced with categories of objects.

Imaging studies in humans, too, appear to support the conjunctive coding idea. One study tested the two theoretical models by considering that the conjunctive coding model predicts that representation of wholes are more than just the sum of their parts, because there is a special unit that represents the whole, above and beyond the units that represent the parts. In contrast, the nonlocal binding model predicts that the representation of the whole would be the same as the sum of the representations of the individual parts (Erez et al., 2016). The researchers used multi-voxel pattern analysis of fMRI data that were collected while people viewed stimuli that included individual constituent parts as well as combinations of parts. The general finding was that regions

in the anterior ventral stream showed a unique pattern of activity in response to whole objects that could not be accounted for based on summing the activation patterns in response to the component parts. This supports the conjunctive coding model, implying that grouping features into whole shapes involves more than simply co-activating the feature representations.

Category Specificity: Are Some Types of Stimuli More Special Than Others?

One of the most hotly debated topics in the study of object recognition is the question of whether there are specific neural modules within the ventral stream specialized for recognizing specific categories of objects. Evidence exists for at least some specialized modules, as illustrated in [Figure 6.19](#) (Kanwisher and Dilks, [2014](#)). One region, known as the [fusiform face area \(FFA\)](#), exhibits a greater response to faces than to other objects. Another region, known as the [parahippocampal place area \(PPA\)](#), appears to process visual information related to places in the local environment. The [extrastriate body area \(EBA\)](#) responds preferentially to images of human bodies and body parts, compared to various inanimate objects and object parts. Finally, a region in the ventral stream of the left hemisphere known as the [visual word form area \(VWFA\)](#) is especially responsive to visual representations of words. We begin our discussion with a focus on the question of face-specific processing in the FFA, and return later to the other specialized modules that are crucial in processing bodies, places, and words.

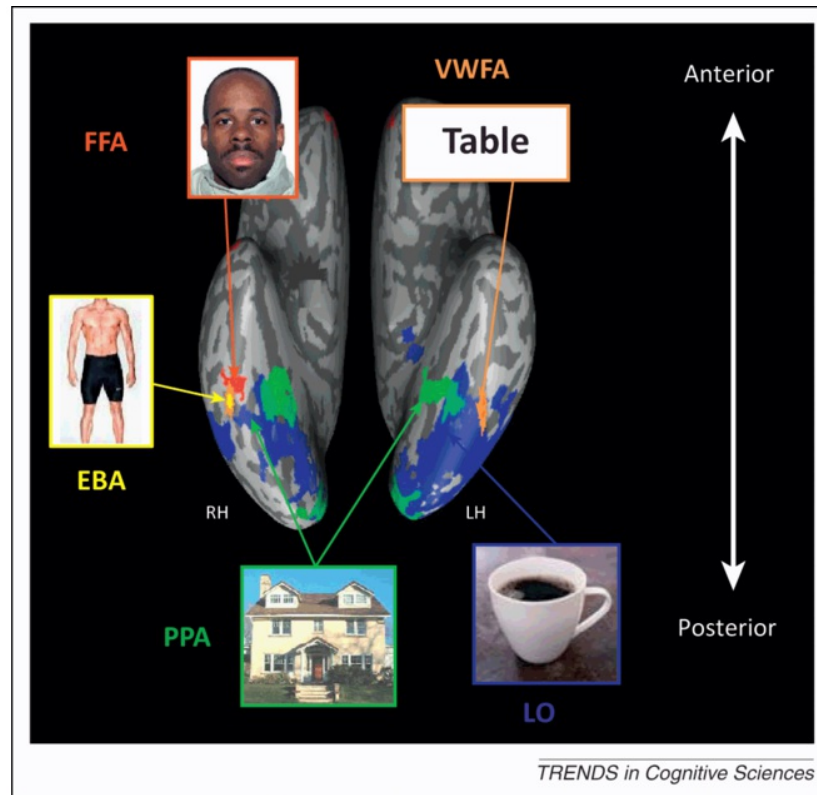


Figure 6.19 The relative locations of the fusiform face area (FFA), the extrastriate body area (EBA), the parahippocampal place area (PPA), and the visual word form area (VWFA).

This view shows the ventral surface of the brain, and for each identified region gives an example of the kind of image to which that region is especially responsive. The lateral occipital complex (LOC), which is responsive to a wide range of visual objects, is also shown for comparison.

(from Behrmann and Plaut, [2013](#))

Nowhere has the debate about category specificity raged more vigorously than over the question of whether the brain contains a face-specific module. Without a doubt, face recognition is an ecologically important task, possibly one of the most important tasks for a primate. The ability to distinguish among people's faces is critical for many aspects of social interaction and communication. Moreover, these abilities have probably been honed over evolutionary time. Whereas humans as a species have known how to read and write for only the last 5,000 years, the ability to distinguish family,

friends, and foes on the basis of facial features has been of great importance for the survival of humans and other primates for millions of years. So, does the brain indeed treat faces differently than other objects? A variety of evidence suggests it does.

Evidence From Other Primates

Single-cell recordings in monkeys provide evidence for a specific neural substrate underlying face recognition. As we've learned already, cells in the inferotemporal cortex can be tuned to highly specific visual information. In some cases, the cells in this region fire specifically in response to faces, regardless of whether the faces belong to monkeys or people (Gross et al., [1969](#), [1972](#)). Notably, these cells do not fire in response to other round objects, such as alarm clocks, or to other emotionally important stimuli, such as snakes. Even more specialized cells in the inferotemporal cortex fire only in response to specific aspects of faces, such as the eyes, or to the components of monkeys' faces only if those components are correctly positioned but not if their positions are scrambled. In some cases, cells are selectively responsive to individual faces, such as that of the experimenter (for reviews, see Gross, [2005](#); Rolls, [2004](#)).

Although it has long been known that individual inferotemporal cells could be face-specific, the single-cell recording technique – with painstaking recording of individual cells in different places – makes it hard to tell if many such cells are clustered together into a specific region of the ventral stream. To address this issue, researchers applied fMRI to monkeys and found face-selective patches of cortex (Tsao et al., [2003](#)). Within these patches, as many as 97% of the individual cells appear to be face-specific (Tsao et al., [2006](#)) (see [Figure 6.20](#)). Moreover, using other imaging methods, researchers have found that face-specific cells are distributed asymmetrically in the monkey brain, with more such cells evident in the right hemisphere (Zangenehpour and Chaudhuri, [2005](#)). These results fit nicely with data from humans indicating that areas of the ventral stream in the right hemisphere are especially important for face recognition.

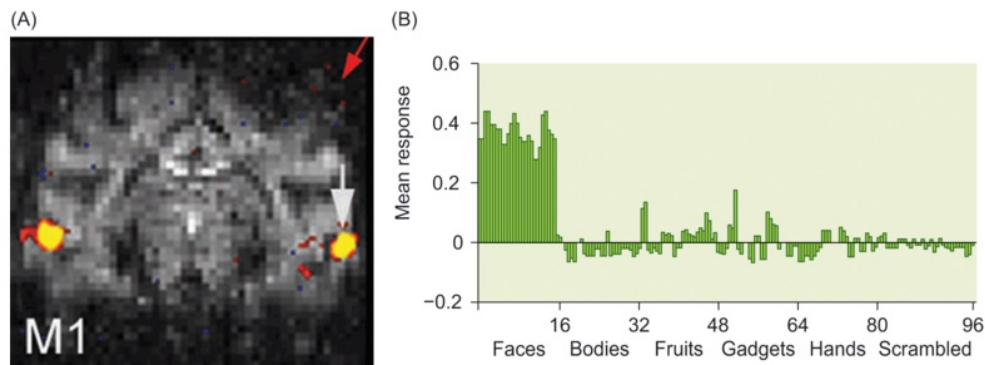


Figure 6.20 Face-selective patches in monkey visual cortex.

(A) fMRI was used to identify regions in macaque monkey brains that were responsive to faces (from Tsao et al., [2006](#)). (B) Recordings from individual cells within these regions show stronger responses to faces than to other categories of objects.

Evidence From Prosopagnosia

Evidence from brain-damaged patients with prosopagnosia also suggests that faces are special. As discussed in [Chapter 2](#), double dissociation is a particularly powerful method for demonstrating that two mental processes can proceed independently of one another, and that they rely on different neural substrates. Such a double dissociation has been observed for face and object recognition. As discussed earlier, people with prosopagnosia have difficulty identifying faces but can recognize other objects with little difficulty. Researchers considered that perhaps people had such deficits just because faces are harder to recognize than objects. However, this explanation seems unlikely, as there are other patients who exhibit the opposite syndrome: they can recognize faces but exhibit agnosia for objects (e.g., Feinberg et al., [1994](#); Moscovitch et al., [1997](#)) (see [Figure 6.21](#)). This double dissociation appears to confirm that face recognition is dissociable from recognition of other objects, and therefore relies on a separate neural system.



Figure 6.21 Picture used to test object and face recognition in patients with agnosia.

A patient was unable to recognize the fruits or vegetables in the pattern but could recognize the face. Together with prosopagnosics, who are unable to recognize faces while still recognizing objects such as fruits, the pattern of performance of this patient helps to demonstrate a double dissociation between object and face recognition.

© Lebrecht Music and Arts Photo Library/Alamy.

Some researchers have questioned whether prosopagnosia is really best defined as a deficit in face recognition, or whether it might be more appropriately described as a deficit in within-category individuation. In other words, when we discuss face recognition, we are usually referring to the ability to tell apart the faces of two individuals (e.g., Susan versus Maria), whereas when we discuss object recognition,

we are usually referring to the ability to tell apart two different types of objects (apples versus bananas) rather than two different instances of that type (apple #1 versus apple #2). At least some prosopagnosics do indeed have difficulty distinguishing among members of other (nonface) categories. In one case report, a farmer who became prosopagnosic could no longer distinguish among the cows in his herd (Bornstein et al., [1969](#); see also Bornstein, [1963](#)).

Yet, there are other case reports in which the ability to distinguish among individual faces is lost but the ability to do so for other categories is preserved. In one case, a patient with prosopagnosia was a car expert, possessing a set of more than 5,000 miniature cars. When researchers showed him 210 pictures of cars, for 172 of the pictures he was able to identify each car's make, model, and year of production (within two years), and of the remaining 38, he correctly identified the company in 31 cases and the model in 22 cases (Sergent and Signoret, [1992](#)). In another case, a patient who became a farmer after becoming prosopagnosic learned to identify the individual faces of his flock of sheep, even though he could not recognize individual human faces (McNeil and Warrington, [1993](#)). Relatedly, a person with developmental prosopagnosia was able to identify many different horses, despite having severely impaired ability to recognize human faces (Weiss et al., [2016](#); for other case studies, see Bruyer et al., [1983](#); De Renzi, [1986](#)). The existence of these dissociations in some (even if not all) cases serves as evidence that face recognition can be disrupted independently of other within-category discrimination abilities, implying that faces are a special category of visual object.

Evidence From Brain Imaging Studies

Because patients with prosopagnosia are so rare, scientists have examined whether converging evidence from brain imaging techniques with neurologically normal people supports the idea that the brain processes faces differently from other objects. A variety of evidence suggests that this is the case.

Recordings of electrical potentials indicate that by about 170–200 milliseconds after the onset of a visual image, the brain responds differently if the image is perceived as a face versus some other object. A particular negative-going ERP brain wave occurring at about 170 ms post-stimulus (i.e., an N170) occurs with greater amplitude when people are asked to view faces compared to other categories of stimuli, such as cars (Rossion and Jacques, 2012). [Figure 6.22A](#) illustrates what the N170 waveform looks like, and [Figure 6.22B](#) shows examples of the kinds of stimuli that typically produce either small or large N170 effects. As seen in the figure, even cartoonish or distorted faces tend to produce a large N170 (although sometimes it is slightly delayed for distorted faces), whereas other categories of objects do not. Although ERP studies cannot be spatially precise regarding the neural origin of the signal source (see [Chapter 3](#)), the N170 peak is maximal at temporal lobe scalp sites, implying that its origin probably lies within the ventral stream.

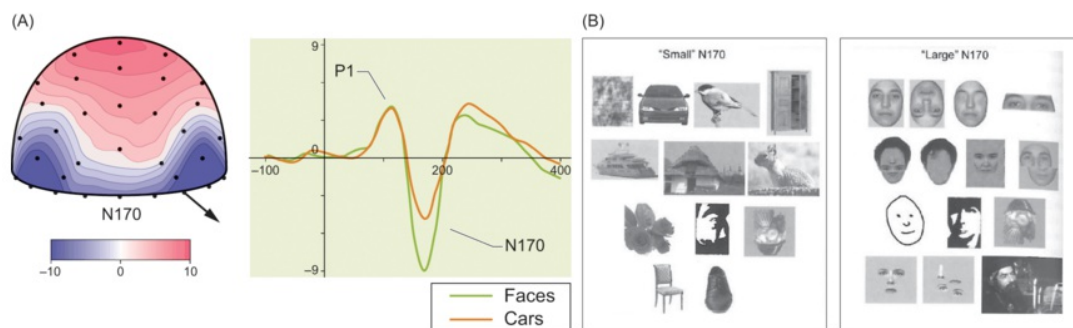


Figure 6.22 The N170 response to faces and other objects.

(A) The N170 is a negative-going peak that appears about 170 ms after the onset of a visual image. Its amplitude is higher when the visual image is a face, and the peak is maximal over lateral sites over the temporal lobes. (B) The kinds of stimuli that produce smaller versus larger N170 peaks.

(from Rossion and Jacques, 2012)

These electrophysiological studies mesh well with those of functional imaging studies of face processing. PET and fMRI studies have identified ventral regions of extrastriate cortex in the right hemisphere as critical for discriminating among the

physical features of faces (Kanwisher et al., [1997](#); Sergent et al., [1992](#)). This region, now referred to as the FFA, is responsive to a wide range of face stimuli (compared to nonface stimuli), such as cartoon and schematic faces as well as photographs of familiar and unfamiliar faces (Kanwisher and Dilks, [2014](#)). Evidence suggests that the organization within the FFA may not be uniform. Rather, some patches of cortex within the FFA are highly selective for faces whereas other patches are less so (Grill-Spector et al., [2006](#)).

Additional evidence, however, indicates that the recognition of faces does not rely only on the FFA, but instead relies on a variety of regions within the ventral stream region working together in concert. For example, an area located earlier in the visual processing stream, known as the occipital face area (OFA), is sometimes identified in brain imaging studies of face perception. The relative locations of the OFA and FFA are shown in [Figure 6.23](#). Because of its earlier position in the ventral processing stream, the OFA is likely to be more involved in earlier stages of perceptual processing of face images, such as identifying the individual parts of a face, while the FFA is more involved in processing the configuration of parts in a face (Liu et al., [2010](#)). Anatomical imaging studies using diffusion tractography have shown a strong anatomical connection between these two areas (Gschwind et al., [2012](#)), suggesting that they are both part of an integrated network for face processing.

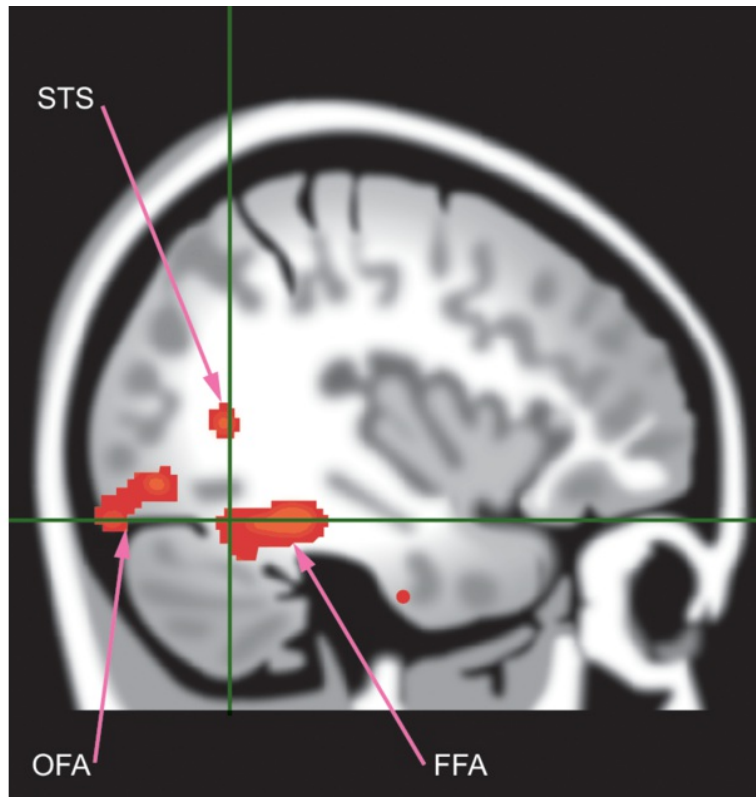


Figure 6.23 Location of major face processing regions in ventral visual cortex.

STS = superior temporal sulcus, OFA = occipital face area, FFA = fusiform face area.

(from Davies-Thompson et al., [2013](#))

Another area, the superior temporal sulcus (STS; see [Figure 6.23](#)), is most important for processing the changeable aspects of the face, such as perception of eye gaze, expression, and lip movement, in contrast to the FFA, which is important for processing those aspects of the face that are invariant and thus helpful for identifying individual people. Individual cells in the STS of the monkey brain are sensitive to gaze and head direction, with most cells preferentially firing to full views of the face with eye contact and profile view of faces with averted gaze (Perrett et al., [1985](#)). In humans, attending to the eye-gaze direction causes greater activity in the STS than in the fusiform region, whereas paying attention to facial identity activates fusiform areas more than superior temporal regions, suggesting a dissociation between these two areas (Hoffman and Haxby, [2000](#)).

STS cells are also sensitive to facial gestures, especially those involving the mouth, such as a grimace, teeth chatter, or threat display (Perrett and Mistlin, [1990](#)). Furthermore, the STS is more activated by videos of facial movements than static images of faces, whereas the FFA and OFA are equally activated by videos and still images (Pitcher et al., [2011](#)). This special role of the STS in responding to facial movements is likely related to its broader role in interpreting movements that have social significance.

Researchers have debated whether these regions are mainly involved in processing faces compared to other categories of visual objects, or whether they are also involved in individuating among specific faces (e.g., Susan versus Maria). At least some evidence suggests that anterior regions of the right temporal lobe may play a specific role in helping to identify a face as belonging to a specific person. For example, anterior regions of the right fusiform gyrus are active only during a face-identification task but not during a gender-identification task, implying that these regions may be specialized for determining facial identity (Sergent et al., [1992](#)). Furthermore, activity in this region, more so than in other ventral visual regions, shows invariance with regard to facial identity, such as activating to distinct half-faces of a given person in the same manner (Anzellotti and Caramazza, [2016](#); see also Anzellotti and Caramazza, [2014](#); Nestor et al., [2011](#)).

All these studies indicate that several areas within occipital and ventral temporal regions are involved in face processing, with the right hemisphere playing a predominant role. In general, posterior regions seem to be important for the perceptual processes that must be performed to create a configural representation of a face (as distinct from other objects) and to extract the invariants of the face that make it unique. In contrast, more anterior regions are involved in linking a particular facial representation to the pertinent biographical information about that person. Finally, regions of the STS are involved in processing those features of the face that change, such as eye gaze and expression, and thus provide critical information for social cues.

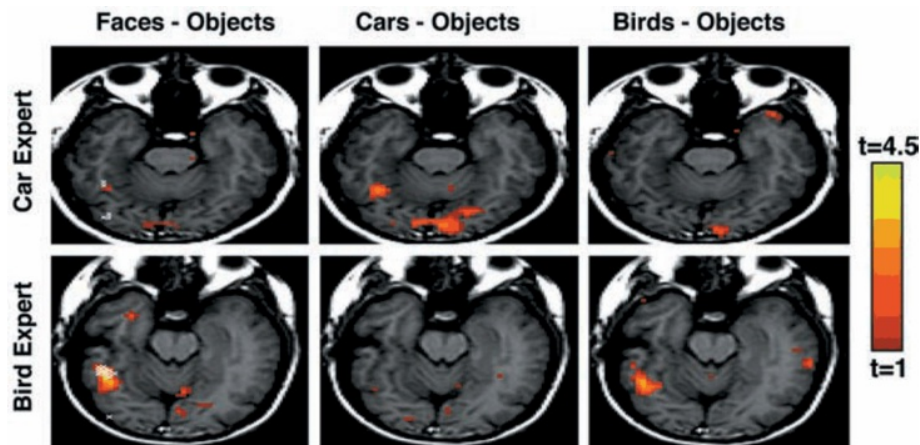


Figure 6.24 The sensitivity of the right fusiform area to expertise in individuating members among a class of objects.

Shown here are patterns of activation for faces, cars, and birds versus other objects in columns 1, 2, and 3, respectively. The top row shows data from a car expert and the bottom row shows data from a bird expert. (The brain slices are shown according to radiological convention in which the right side of the brain is on the left side of the image.) Notice that in the car expert, a similar region is activated for faces and cars, while for the bird expert, a similar region is activated for faces and birds.

Source: Adapted by permission from Macmillan Publishers, LTD: Gauthier, I., Skudlarski, P., Gore, J.C., Anderson, A.W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience*, 3(2), Figure 3, page 193.

If Faces Are Special, Why Are They Special?

Converging evidence indicates that regions of the human and monkey brain are especially responsive to faces. But what makes faces special? Are primates hard-wired such that the FFA is innately programmed for this particular category of visual stimuli, because faces are so important evolutionarily? Can other stimuli activate the FFA, and, if so, what does that tell us about the specialization of this brain region?

One possibility that may have already occurred to you is that we are highly experienced with faces, more so than with many objects. In particular, from early in life we learn to distinguish between the faces of many different individuals, whereas most of

us do not learn to distinguish between hundreds of different trees, chairs, or cars. Could the FFA really just be an area that helps to make fine distinctions among objects within a category?

Neuroimaging studies support the idea that expertise with a particular category leads to increased activity in the FFA. In one study, 11 car experts and 8 bird experts, who on average had 20 years of experience identifying such items, were asked to decide whether a previously seen item (car/bird) was the same as the present one. The car experts exhibited greater activity in the “face” region for cars than for other objects, while the bird experts exhibited greater activity in this region for birds than for other objects, as illustrated in [Figure 6.18](#) (Gauthier et al., [2000](#); though see Grill-Spector et al., [2004](#)).

Furthermore, activation in this “face” region increases as people become better trained to recognize novel objects. In one study, individuals were trained to become expert at recognizing novel objects, known as “greebles” (see [Figure 6.25](#)). Greeble experts but not greeble novices activated the right FFA when viewing the greebles. Furthermore, the activation in the right FFA for upright compared to inverted greebles increased with training (Gauthier et al., [1999](#)). Remember that the inversion effect is taken as an index of configural processing. These findings have led some to suggest that the FFA is really a “flexible fusiform area” specialized for subordinate-level visual processing (i.e., differentiating individuals), which becomes automatic with expertise (Tarr and Gauthier, [2000](#); but see McKone et al., [2006](#), for a dissenting viewpoint).

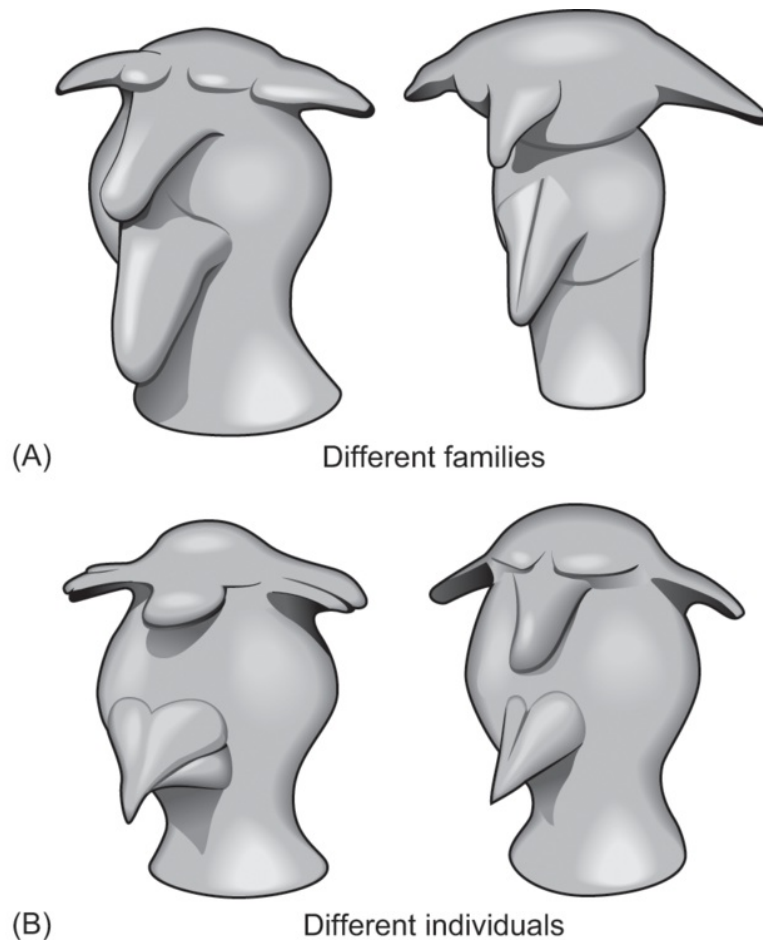


Figure 6.25 Other objects that can activate the fusiform face area.

Shown here are “greebles,” somewhat face-like objects that can activate the fusiform face area after individuals gain expertise in individuating such objects. (A) Two greebles from different “families,” which are differentiated by their large central part. (B) Two greebles from the same family. Their central portions are similar, but the smaller parts are different. As an indication of expertise, greeble experts can distinguish between two members of the same family as quickly as they can distinguish between two greebles from different families.

What are we to make of the evidence that the FFA is sensitive to greebles in greeble experts, to birds in bird experts, and to cars in car experts? Does it mean that faces aren't special? Some critics have pointed out that the greebles, and possibly bird and car images as well, are somewhat face-like, in the sense that they have a configural structure (Kanwisher, [2000](#)). Therefore, perhaps the increasing involvement of the FFA

with expertise in cars, birds, or greebles occurs because people rely on their innate face processing module to individuate these other classes of objects.

So, is the basic specialization of the FFA really for configural processing (required for individuating objects) but masquerading as a “face” area simply because we have more experience with faces than other objects? Or is the FFA innately specialized for processing faces, but also relied upon for other stimulus categories when they become more and more face-like?

For a number of reasons, the latter interpretation is more likely to be correct (Kanwisher and Yovel, [2006](#)). First, a brain imaging study showed that the FFA is no more activated by configural tasks than part-based tasks, while confirming that it is more activated by faces than other categories of objects (Yovel and Kanwisher, [2004](#)). This evidence suggests that the selectivity of the FFA is for the stimulus category of faces, not for the process of recognition through configural processing. Second, evidence we’ve already reviewed from prosopagnosic patients suggests that the neural mechanism allowing us to differentiate among individual faces is independent from the mechanism allowing us to distinguish among individuals of other classes, such as cars or sheep. Interestingly, two prosopagnosic patients have been reported to exhibit normal learning of greebles despite showing severely impaired learning of new human faces, suggesting that human face recognition is still “special” even above and beyond the within-category individuation that is necessary for greeble recognition (Rezlescu et al., [2014](#)). Nevertheless, the fact that the FFA may also be used when perceiving other objects provides interesting clues about the flexibility of the inferotemporal cortex (Bukach, Gauthier, and Tarr, [2006](#)).

Bodies, Places, and Words Are Special Too

Most research on category specificity in object recognition has focused on the study of faces as a special category. However, in recent years, investigators have also begun to

understand how the visual system represents other categories of visual objects, such as parts of the body, visual representations of places, and visually presented words.

It should not come as a surprise that visual representations of the body are also of paramount significance in the brain – consider that throughout the history of art, representations of the human form are ubiquitous. For both humans and other primates, it is crucial to recognize and interpret information conveyed by the bodies of other members of one's species. This involves recognizing not just their facial identities and expressions, but also recognizing their bodily movements, postures, stances, and gestures (Peelen and Downing, [2007](#)). Indeed, the perception of other people's bodies is crucial for social cognition. The ability to visually represent another person's posture and actions can give us insight into that person's state of mind and intentions toward us.

Behavioral studies have shown that our perceptual processing of bodies may be similar in some ways to our processing of faces. For example, the recognition of bodies appears to be based on configural information, just like the recognition of faces. This claim is supported by evidence that inversion disrupts the recognition of bodies; in fact, the effects of inversion are similar for body postures as for faces, with both showing a larger inversion effect than nonbiological categories such as houses (Reed et al., [2003](#), [2006](#)).

Research with other primate species has identified body-specific neural responses in regions of the temporal lobe. Single-cell recording studies dating back several decades demonstrated that individual cells in the monkey's temporal lobe are especially responsive to specific body parts, such as hands (Gross et al., [1972](#)). Confirming these results with fMRI in the macaque monkey, researchers found body-responsive areas in regions of the temporal cortex that are adjacent to face-responsive areas (Pinsk et al., [2005](#)).

Converging evidence from human studies also supports the claim that certain regions are especially sensitive to visual images of bodies. For example, one study recorded electrical responses from the temporal lobe in the right hemisphere of a patient about to

undergo surgery for epilepsy (Pourtois et al., [2007](#)). These researchers found a response to images of bodies that was greater than the response to other categories of images, such as faces, nonhuman mammals, and tools. Another study disrupted activity in a subregion of the temporal lobe using TMS, and found that this interfered with the ability to distinguish between bodily forms, such as hand and leg postures (Urgesi et al., [2007](#)).

Human imaging studies using fMRI have provided more information about the location of body-sensitive regions within visual cortex. The current understanding is that there are actually multiple areas that are responsive to images of bodies (e.g., Weiner and Grill-Spector, [2011](#)). The extrastriate body area (EBA) is located in Brodmann area 18 in the occipitotemporal cortex (look back on [Figure 6.19](#)). Interestingly, this area is near area MT, a region that is especially sensitive to motion; perhaps this adjacency reflects the importance of connecting the image of a bodily form with its motion. Another body-sensitive region is called the fusiform body area, and it is located in the fusiform gyrus just adjacent to the fusiform face area that we have already discussed. High-resolution imaging studies have demonstrated that face-sensitive and body-sensitive subregions of the fusiform gyrus can be distinguished from one another (Schwarzlose et al., [2005](#); Weiner and Grill-Spector, [2013](#)) (see [Figure 6.26](#)).

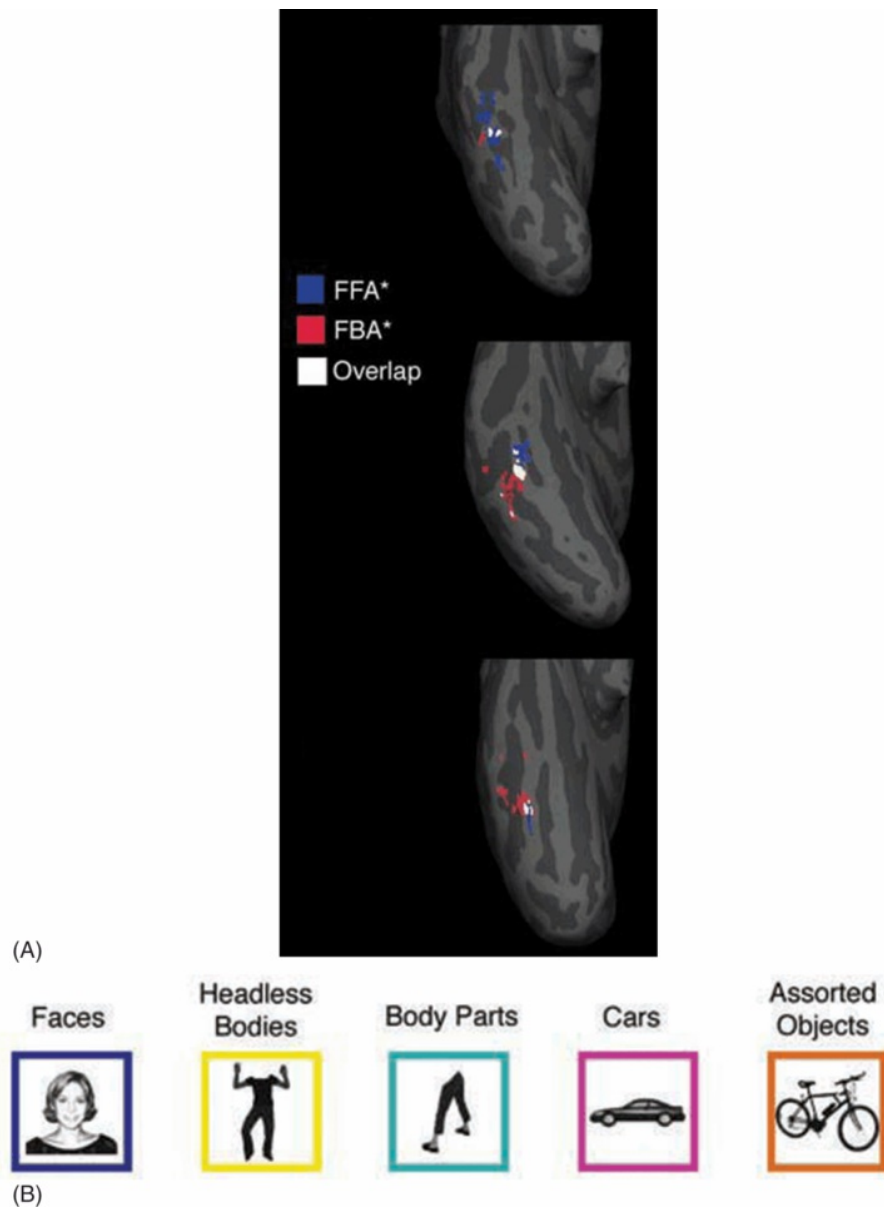


Figure 6.26 Separable regions of activation in the fusiform gyrus in response to faces and to faceless bodies.

Part (A) shows activity in the fusiform face area (FFA) and fusiform body area (FBA) for three different participants. The view is of the ventral surface of the posterior right hemisphere. Part (B) shows stimuli that were used in the experiment. The FFA was defined as the region in which activity was greater for faces than for cars and other objects. The FBA was defined as the region in which activity was greater for headless bodies or other body parts than for other objects. Areas labeled as “Overlap” in part (A) were activated by both faces and bodies more than by other kinds of objects.

Together, the face-sensitive and body-sensitive subregions of the ventral cortex can represent a whole person. Neuroimaging studies have found that the pattern of activity across the fusiform gyrus in response to the image of a whole person can be predicted by summing together the responses of face-sensitive subregions to the image of the face alone plus the responses of body-sensitive subregions to the body alone (Kaiser et al., [2014](#)). These findings remind us that regions responsive to specific object categories (such as faces and bodies) work together to represent a whole image.

While faces and bodies have received the most attention as special categories of visual images, other research has found that there are also circumscribed regions that respond best to visual images of places in the environment. The parahippocampal place area (PPA), located in a ventral cortical region bordering the hippocampus, can be seen on [Figure 6.19](#). Imaging studies indicate that it responds particularly strongly to visual scenes such as landscapes, rooms, houses, or streets (Epstein, [2008](#)). We will return to the role of this region in spatial navigation in the [next chapter](#), which focuses on spatial cognition.

In addition, a ventral stream region in the left hemisphere appears to be especially responsive to visually presented words (Dehaene et al., [2002](#); Dehaene and Cohen, [2011](#)). The visual word form area (VWFA) is illustrated in [Figure 6.19](#). Anatomically, the VWFA has stronger connections with left-hemisphere language areas than does the fusiform face area (Bouhali et al., [2014](#)). In general, the typical left-hemisphere location of the VWFA complements the typical right-hemisphere location of the FFA, consistent with long-known hemispheric specialization for processing words versus faces.

Like the FFA, EBA, and PPA, the VWFA is associated with differentially strong responses to a particular category of visual images, in this case words. However, an interesting difference is that the VWFA must gain its specialization due to experience, rather than to innately preprogrammed preferences. Unlike the recognition of faces, bodies, and places, visual word recognition (reading) is a relatively recent development in human history, forming part of our cultural heritage but not part of our evolutionary heritage. Children in literate societies do not typically learn to read until

school age, and many children and adults in nonliterate societies do not read at all. As you might expect, the VWFA's special response to visual words is only present in people who can actually read those words (Dehaene et al., [2010](#); Glezer et al., [2015](#)). We will return to the role of the VWFA in reading in [Chapter 8](#), our chapter on language. In the meantime, we can interpret this region as another category-specific ventral stream region, albeit one whose specialization is acquired through learning.

These category-specific processing regions in the ventral stream reinforce the importance of the ventral stream in visual object recognition in general, and further imply that ventral stream areas are parcellated into functional units in order to represent critical kinds of objects. However, as in all areas of cognitive neuroscience, it is good to be wary of overly strict localizationalist views, which rigidly attribute particular functions to particular regions. While there does appear to be specialization of subareas within the ventral stream, these areas are not “pure.” For example, while the FFA is clearly a key player in face recognition, it also responds (to a lesser extent) to other visual objects; conversely, areas besides the FFA also respond to some extent to faces.

Moreover, some researchers propose that the processing of visual objects occurs in a more distributed manner across the entire ventral visual processing stream. According to this view, specific object categories are each associated with a specific pattern of activation across this wide expanse of neural tissue. Evidence for this idea comes from multi-voxel pattern analysis, which, as we discussed in [Chapter 3](#), is a means to examine not just the degree of activation in certain brain regions, but also the pattern or mosaic of activation. In an initial study using this method, participants viewed different examples of items within specific categories, such as faces, houses, chairs, and shoes (Haxby et al., [2001](#)). Each category produced a signature pattern of activity, such that all items within a category (e.g., all chairs) exhibited a similar pattern. Moreover, the signature varied significantly between item categories (e.g., chairs versus shoes), so much so that the scientists could use the pattern of brain activity to determine what type of item a person was viewing with 96% accuracy!

At this point, you might be thinking, “Well that’s not so surprising – the signature pattern of activity for faces probably involves activation mainly in the FFA and for houses mainly in the PPA.” To address this possibility, the scientists determined the brain regions that responded maximally to one category, say faces, and those that responded maximally to another category, say houses. They then removed those areas from consideration in their analyses, and went back to determine whether the pattern of activity in the remaining areas of the ventral visual processing stream could distinguish between the object categories. Once again, the pattern of activity successfully differentiated between categories. Therefore, they argue that information about specific visual categories is encoded in a distributed manner across ventral cortex, rather than being strictly localized to compartmentalized areas.

This viewpoint, involving more distributed rather than localized representations, intriguingly suggests a mechanism whereby object recognition could occur for many visual categories, including those that are learned over a lifetime. If we had to have a specific dedicated visual region for each object category, we might soon run out of space in our brains, especially as we grow and learn about new items and objects in the world! Having a distributed representation allows for a multitude of different categories to be encoded by the brain.

One challenge for the distributed-processing viewpoint is identifying organizing principles that explain why certain categories have the distributed patterns of activation that they do. Research suggests that the more similar visual items are, the more similar are their patterns of activity across the brain (see [Figure 6.27](#); Kriegeskorte et al., 2008). Moreover, these patterns of activation appear to be somewhat consistent across people, suggesting that the patterns are not simply random or idiosyncratic, but reflect some fundamental principles. However, at present it is not clear exactly what those principles might be, for example, whether the distributed patterns are organized according to some aspects of visual complexity or configurational groupings (Coggan et al., 2016). As in other areas of cognitive neuroscience, we must balance the desire to locate functions to particular areas of tissue with the understanding that complex

information processing is likely to be distributed across regions rather than neatly circumscribed within any one region (see Behrmann and Plaut, [2013](#), for further discussion).



Figure 6.27 Similarity of multi-voxel patterns of activity for objects in inferotemporal cortex.

Plotted here are the similarities between objects as discerned by the pattern of activity they evoke in inferior temporal cortex. The closer objects are represented on the figure, the more similar are the patterns of brain activity that they evoked. Notice that the pattern for natural objects tends to be similar (mainly on the left side of figure) and likewise for human-made objects (mainly on the right side of the figure). Also notice clustering for specific object categories, such as faces (bottom left) and places (bottom right).

(from Kriegeskorte et al., [2008](#), figure 2A, page 1130)

Object Recognition in Tactile and Auditory Modalities

As we have already noted, the study of human perception has been predominantly centered on understanding the visual modality, because vision is such a dominant sense in humans. However, we can also recognize objects by other senses, such as hearing and touch. For example, if you closed your eyes, you could still recognize the sound of an ambulance or the feel of your favorite coffee mug in your hand.

In this section, we consider how object recognition in other modalities can be disrupted, as well as current issues in understanding how object recognition may occur across different senses. Similarities in brain organization emerge across modalities. For example, across modalities, early cortical areas (such as primary auditory cortex) code basic features, whereas higher-level areas are critical for organizing sensations into representations of recognizable objects. When these higher-level regions are disrupted by brain lesions, deficits in object recognition result.

Agnosias in Other Modalities

We focused on visual agnosia in the first part of this chapter, but agnosias can occur in other modalities as well. For example, [auditory agnosia](#) is characterized by normal processing of basic auditory information but an inability to link that sensory information to meaning, despite the fact that other cognitive functions such as attention, memory, and language appear to be normal (see Slevc and Shell, [2015](#), for review). Like visual agnosias, auditory agnosias are quite rare. Patients with auditory agnosia can perceive the occurrence of a pure tone (i.e., a tone of a single frequency), and they do so at loudness thresholds generally equivalent to those of the average person without agnosia. However, when a person with auditory agnosia hears a complex sound, he cannot classify it.

Auditory agnosia usually manifests in one of three ways. In [verbal auditory agnosia](#) (also known as [pure-word deafness](#)), words cannot be understood, although the ability

to attach meaning to nonverbal sounds is intact. The person can read, write, and speak normally, an indication that this condition is not a disorder of linguistic processing. However, patients with this type of auditory agnosia complain that although they know a noise has occurred, speech sounds like “an undifferentiated continuous humming noise without any rhythm” or “like foreigners speaking in the distance.”

Likewise, in [nonverbal auditory agnosia](#), which is rarer than verbal auditory agnosia, the ability to attach meaning to words is intact, but the ability to do so for nonverbal sounds is disrupted. Such a patient knows that a sound has occurred but cannot categorize it, for example as a car horn, a dog bark, or a lawn mower. This difficulty can be quite a problem in real life. For example, if a car’s driver is honking a horn as a warning for people to move out of the way, an individual with auditory agnosia would hear a noise but might not hurry across the street, because the sound was “unintelligible, sort of like how I remember crickets chirping or static on a telephone line.” In [mixed auditory agnosia](#), the ability to attach meaning to both verbal and nonverbal sounds is affected, although the patient can determine whether two sounds are identical or different and whether one sound is louder than the other. That is, in these patients the ability to hear the sounds is intact, and they are not deaf.

Agnosia can also occur for touch information. [Somatosensory agnosia](#), or [tactile agnosia](#) (sometimes referred to as astereognosia), is a condition in which a person is unable to recognize an item by touch but can recognize the object in other modalities (e.g., Reed et al., [1996](#)). As with other agnosias, two types have been proposed, one in which the affected person has an inability to use tactile information to create a percept, and another in which the percept is more or less intact but cannot be associated with meaning. This latter agnosia is sometimes called [tactile asymbolia](#) because the tactile information cannot be linked to its symbolic meaning (e.g., a small metal object that is big at the top and thin at the bottom with a jagged edge cannot be linked to the concept of a key).

The existence of agnosia in the auditory and tactile modalities illustrates that deficits in recognition can occur even when visual recognition is intact. This, in turn, reminds us that recognition can occur independently through several different senses. Yet, in everyday life, we often receive parallel cues to recognition simultaneously from multiple modalities, such as when you see the face of your cat, hear her purr, and feel her soft fur. We next consider several approaches to understanding the relationship between recognition through visual, tactile, and auditory senses.

Tactile Object Recognition

One perspective on object recognition emphasizes the commonalities in recognition through vision and touch. For example, people who are trained to recognize novel objects by touch show inversion effects, implying configural processing, just as seen for expertise in visual object recognition (Behrmann and Ewell, [2003](#)). In addition, both touch and vision provide information about the three-dimensional shape of an object in a way that auditory information does not. To illustrate, imagine an alarm clock of a particular shape and size. You could either see or feel its shape and size, but just hearing the sound of the alarm clock's ring would not provide information about its shape and size.

Tactile object recognition appears to rely on its own set of unique neural regions, as well as activating regions shared with vision. Palpating (feeling) real objects compared to nonsense objects results in activity in secondary somatosensory regions as well as the insula (Reed et al., [2004](#)), areas not activated for visual object recognition. Nonetheless, this study as well as others (Amedi et al., [2001](#)) also found activity in the LOC, a region known to be important in the visual perception of objects, even though the objects were out of sight. The LOC was not activated by feeling textures such as sandpaper and fur, indicating that the response was specific to objects rather than to any recognizable tactile sensations, nor was it sensitive to sounds associated with specific objects, such as the sound of a hammer or a helicopter (Amedi et al., [2002](#)). This result

indicates that the LOC region codes object properties that are shared between vision and touch but not audition.

Yet, evidence from clinical neuropsychology suggests that the LOC is not likely to be necessary for perception of objects via touch. A case study reported a patient with complete LOC damage and yet normal tactile object recognition (Snow et al., [2015](#)). This finding implies that the LOC is primarily a visual area. While the LOC may be most important in linking tactile information with vision, it is not part of the critical neural substrate required for tactile recognition.

Auditory Object Recognition

Although vision and touch may have certain properties in common that hearing does not appear to share, hearing can also be used to recognize objects. As we learned in [Chapter 5](#), higher-level areas of auditory cortex are crucial in auditory pattern recognition. For example, recognizable auditory sounds (water dripping, egg cracking, horse galloping) evoke greater activity in the middle temporal gyrus than do those same sounds played backward, which makes them unrecognizable (Lewis et al., [2004](#)). Researchers have also examined whether certain categories of auditory objects activate different regions of auditory cortex. In one study, participants listened to two categories of sounds, animal vocalizations (e.g., bird song, horse whinny) and tool-related sounds (e.g., sound of a hammer, typewriter, stapler). Animal vocalizations activated the superior temporal gyrus bilaterally, whereas tool sounds activated numerous areas in the left hemisphere, including motor areas (Lewis et al., [2005](#)). Intuitively, it makes sense that tool sounds would activate motor areas, because the sound of a typewriter may prime the participant to think about the action of typing, whereas the sound of a bird would not necessarily prime any particular motor action.

The recognition of human voices in the auditory modality shares many parallels with the recognition of human faces in the visual modality (Yovel and Belin, [2013](#)). In both cases – the voice and the face – we use the information to identify a particular person (“Amanda” or “Drake” or “mom”), which is critical in social interaction. Indeed,

voices form a special category of auditory objects, just as faces form a special category of visual objects. Studies in monkeys have identified voice-selective regions within the superior temporal lobe, that is, regions that respond preferentially to monkey voices compared to recognizable nonvocal sounds (Perrodin et al., [2011](#); Petkov et al., [2008](#)), a finding confirmed by human imaging studies (e.g., Moerel et al., [2012](#)). Voice recognition can also be selectively disrupted (even with other sound recognition intact), either by transient TMS to the superior temporal lobe (Bestelmeyer et al., [2011](#)) or by acquired brain damage (Neuner and Schweinberger, [2000](#)).

Ultimately, voice recognition and face recognition must be linked together, as they both are related to establishing a particular person's identity. Hearing the sound of someone's voice can lead us to visualize the face of that person, for example. As we saw with tactile object recognition, visual areas may be co-activated when recognizing voices. One study found that the voices of familiar people activate the FFA more than the voices of unfamiliar people, even when no face is presented at the same time (von Kriegstein et al., [2005](#)). When listening to the voices of familiar people, activity in the FFA is coupled with activity in voice-specific regions of the superior temporal sulcus (Belin et al., [2000](#)). However, also as with tactile object recognition, these regions do not appear to be the critical neural substrate for recognizing voices. Remember that prosopagnosic subjects are often able to recognize people by their voices but not by their faces, meaning that the damaged region in prosopagnosia is essential for face recognition but not voice recognition.

What Versus Where Across Modalities

One commonality across all the different senses is that they must distinguish “what” and “where” – what an object's identity is and where it is located. In the visual system, there is a major dissociation between these functions, with the ventral stream primarily concerned with the “what” problem and the dorsal stream concerned with the “where” problem. We learned in [Chapter 5](#) that some researchers have also proposed a “what

versus where” distinction in the auditory system, although evidence for this dissociation is not as clear for audition as it is for vision. A dissociation between coding for object identity and location has also been reported for touch information. For example, when participants are required to mentally rotate a tactile object (a spatial task), the parietal lobe is activated, whereas when they must distinguish the identities of tactile objects, the lateral occipital complex is activated (Prather et al., [2004](#); see also Reed et al., [2005](#)). Thus, the distinction between “what” and “where” pathways in the brain seems to be a basic organizational feature that transcends any specific modality.

As we have seen in this chapter, the problems posed by object recognition in any modality are astounding – and yet our brains solve these problems, recognizing thousands of objects across many different viewing conditions, linking the sensory images of those objects to stored knowledge and meaning, and combining information across modalities to fully comprehend an object in an instant. While the convergence of human imaging, single-cell recording, and patient studies has led to progress in understanding the brain systems underlying object recognition, researchers are still far from fully unraveling the puzzle. Still, recognizing object identities is only one part of the problem that the brain has to solve. Another major challenge is spatial cognition, that is, representing where objects are located in the environment, which we explore next in [Chapter 7](#).

In Focus: Visual Imagery: Seeing Objects With the Mind’s Eye

Have you ever imagined yourself on a tropical island in the Caribbean? Can you see the long, white, sandy beach? The blending of the water’s colors from pale green to jade to aquamarine to royal blue? The palm trees with their fronds waving in the breeze? And, to complete the picture, your latest romantic interest looking perfectly enticing in an ever-so-alluring bathing suit? If so, then even though our discussion of objects has centered on recognizing objects in the real

world, you realize that we also have the ability to examine and manipulate objects in our mind's eye by mental imagery.

The nature of mental imagery had historically been the subject of a long-running debate, the resolution of which was based, in part, on data from cognitive neuroscience (see Pearson and Kosslyn, [2015](#)). Decades ago, the researcher Stephen Kosslyn proposed that mental imagery is much like visual processing, except in the mind's eye. Some support for this position came from behavioral studies in which Kosslyn found that the time needed to "see" particular parts of an image was proportional to the distance that we would expect the mind's eye to have to move to get to that part. For example, participants were told to imagine an item (e.g., an airplane) and to focus on one end (e.g., the propeller). Then they were given the name of a particular feature to look for ("the tail") and instructed to press a button when they could see it. People took longer to press the button if the feature was located at the other end of the imagined item (e.g., the tail) than if it appeared in the middle (e.g., the wing), consistent with the idea that mental imagery is similar to vision.

An alternative perspective was that we don't actually draw mental images (Pylyshyn, [1973](#), [1981](#)). According to this view, the results of Kosslyn's experiment could just as easily be explained by propositional knowledge. Propositional knowledge describes entities (e.g., a propeller, a wing), their relations (next to, behind), their properties (long, silver), and their logical relations (if). According to this view, a person takes less time to decide about the wing than the tail because the person must remember only that the wing is behind the propeller, which is fewer propositions than remembering that the tail is behind the wing, which in turn is behind the propeller.

The arguments for and against each theory were debated for more than a decade, until neuroscientific evidence was brought to bear to resolve what previously had been a relatively intractable question. Researchers reasoned that

if imagery does rely on producing a picture in the mind's eye, it should require some of the same neuronal machinery required by vision (e.g., Farah, [1988](#)). Alternatively, if imagery tasks can be performed simply by resorting to propositional knowledge about objects in the world, then the memory or semantic processing areas of the brain should be active, but visual areas should not.

Studies of regional brain activation, as well as studies of “reversible lesions” caused by TMS, indicate that visual areas play a major role in imagery. For example, if imagery relies on the visual cortex, some relationship should exist between the size of the imagined object and the area of visual cortex that is activated. This finding would be expected because, as discussed in [Chapter 5](#), visual space is mapped onto visual cortex in a retinotopic manner. Consistent with this hypothesis, investigators found that when a person was imagining small letters in the center of the mind's eye, activation was greatest in posterior regions of the medial occipital lobes, which is the region that processes information from the fovea. In contrast, when a person was imagining larger letters, activation occurred over a larger area of visual cortex that included more anterior regions, which is where more peripheral regions of visual space are processed (Kosslyn et al., [1993](#); Slotnick et al., [2005](#)).

In another creative experiment, researchers recorded brain activity using fMRI while participants either viewed an X or an O or imagined either of those two stimuli (Stokes et al., [2009](#)). The researchers trained a computer program to classify each trial as an X or an O, based on the different patterns of brain activity in the lateral occipital complex during actual visual perception of the X versus the O. The computer program was then able to generalize its learning based on the perception trials and apply it to the imagery trials. In other words, the computer program could tell, at above-chance levels, if the participant was imagining an X or an O, based on the similarity of the brain activity to that

shown when the participant was actually seeing the X or the O. These findings further indicate that perception and imagery share some common basis (see also Albers et al., [2013](#)).

Additional studies have shown that the perception–imagery overlap in visual cortex extends to specific categories of visual images, such as faces, bodies, and places. As we have learned, visual stimuli from these categories activate different subregions of the ventral stream, such as the FFA, EBA, and PPA. Recent research has found that imagining stimuli of these same categories (faces, bodies, and places) results in differentiated patterns of activity across the FFA, EBA, and PPA in a way that mirrors the patterns elicited when the stimuli are actually perceived rather than imagined (Cichy et al., [2012](#)). For example, the FFA responds more strongly to mental imagery of faces compared to places, whereas the PPA responds more strongly to mental imagery of places compared to faces.

With the advent of TMS, it has been possible to disrupt processing of visual areas. If imagery relies on visual processing regions of the brain, then disrupting those areas should also disrupt the ability to use imagery. To test this premise, Kosslyn and colleagues first had participants memorize four sets of lines. Then, participants were given auditory information about which two sets of lines to compare and along what dimension (e.g., relative length, width, orientation, or spacing between them). During the imagery condition, participants exhibited increased activity in V1 (BA 17), compared to a control condition in which no imagery was required. Researchers then applied TMS while the individuals were performing either the imagery task or a perceptual version of the task in which the stimuli were kept in front of the individual. TMS interfered with both perception and imagery, suggesting that primary visual areas are critical for this function (Kosslyn et al., [1999](#)).

Does this mean that the regions of the brain involved in perception and imagery are identical? If so, then how would we ever be able to tell the

difference between what we experience in a particularly vivid dream and our everyday perceptual experience? Although neuroimaging studies suggest a high degree of overlap, there are areas activated uniquely for each (Kosslyn et al., [1997](#)). Furthermore, there are case studies of patients who have impaired object perception but intact imagery and also the converse, patients with disrupted imagery but intact perception (Behrmann et al., [1994](#); Farah et al., [1988](#)). These findings suggest that at least some aspects of the neural control of imagery and perception must be separable, although in most situations they may rely on similar perceptual regions of the brain.

While one basic question about mental imagery – whether it draws upon perceptual regions of the brain – appears to have been answered, many unanswered questions remain. For example, some researchers are investigating how individual differences in imagery ability are correlated with anatomical and functional differences in brain regions supporting perception (e.g., Bergmann et al., [2015](#)). Others are examining how multi-modal (e.g., audiovisual) imagery takes place (e.g., Berger and Ehrsson, [2014](#)), as well as how higher-level control regions of the brain (which we will learn more about in [Chapter 11](#)) contribute to the initiation and control of mental imagery in the absence of perceptual stimulation (e.g., Daselaar et al., [2010](#); Zvyagintsev et al., [2013](#)). Meanwhile, until these issues are addressed: dream on!

Summary

The “What” Ventral Visual System

- This brain system, which plays a major role in the ability to recognize objects, courses ventrally from the occipital regions toward the anterior pole of the temporal lobe.

- Single-cell recordings in monkeys indicate that cells located more anterior in the ventral visual processing stream fire to specific forms, have larger receptive fields than earlier visual areas, and are sensitive to color, attributes that are all helpful to recognizing specific objects.

Deficits in Visual Object Recognition

- Apperceptive agnosia is an inability to process basic features of visual information that precludes perception of even the simplest forms (e.g., an “X”).
- In associative agnosia, the basic perceptual properties of visual information can be processed but not to a high enough degree to allow for object recognition.
- Whereas apperceptive agnosia is associated with diffuse bilateral damage near and extending into occipital regions, associative agnosia is associated with bilateral damage near the occipitotemporal border.
- Prosopagnosia is the inability to recognize faces but not other objects, and can occur after damage to certain areas of the ventral stream or during development with no known brain injury. Some aspects of faces can be recognized implicitly, even though the person cannot identify or otherwise classify the face.
- Some disorders affect the ability to recognize items within certain categories (e.g., fruits and vegetables), but not other categories (e.g., items manufactured by humans). In most cases, these deficits reflect semantic memory problems, rather than strictly visual deficits, because they affect the ability to define the affected objects as well as the ability to visually recognize them.

Theoretical Issues in Object Recognition

- Although some cells in the ventral stream appear to have high selectivity for certain complex stimuli, objects are most likely coded by dynamic patterns of activity across populations of cells.

- One major problem the visual system must solve is recognizing objects despite variation in their size, position, lighting, and viewpoint. For example, researchers are still working to understand how viewpoint-independent representations can be constructed from cells that mainly respond best to specific viewpoints.
- Both individual features and their holistic configuration are important in object recognition. The left hemisphere is specialized for featural recognition, whereas the right hemispheric is specialized for configural recognition. We tend to rely on configural information more for objects with which we have expertise.
- Evidence from brain-damaged individuals, neuroimaging, and electrophysiology indicate that faces are processed differently than other classes of objects. Recent evidence indicates that perception of other body parts, places, and words may also take place in specialized brain regions or as unique patterns of activation across the expanse of the ventral visual processing stream.

Object Recognition in Other Modalities

- Auditory agnosia impairs the ability to recognize verbal sounds, nonverbal sounds, or both.
- Somatosensory, or tactile, agnosia, impairs the ability to recognize items by touch.
- The lateral occipital complex appears to link tactile and visual representations of objects.
- Voice-specific regions in the superior temporal lobe are analogous to face-specific regions in the ventral temporal lobe.
- Recognition of an object in one modality may prime a representation of that object in other modalities as well.

Chapter 7

Spatial Cognition



[The Dorsal Visual System for Spatial Cognition](#)

[Anatomy of the Dorsal Stream](#)

[Cellular Properties in the Dorsal Stream](#)

[Coding for the Three Dimensions of Space](#)

[Distinguishing Left from Right](#)

[Depth Perception](#)

[Spatial Frames of Reference](#)

[Neural Coding of Reference Frames](#)

[Dissociability of Reference Frames](#)

[Categorical Versus Coordinate Spatial Relations](#)

[Motion Perception](#)

[Specific Neural Regions for Motion Perception](#)

[Incorporating Knowledge of Self-Motion](#)

[Accounting for Movement of the Eyes](#)

[Accounting for Movement of the Body](#)

[Space and Action](#)

[Constructional Abilities](#)

[Optic Ataxia](#)

[Neural Mechanisms of Sensory-Motor Integration](#)

[Spatial Navigation](#)

In Focus: Are Numbers Spatial?

Navigational Skills

Neural Coding for Spatial Environments

Parahippocampal Place Area

Retrosplenial Cortex

Medial Temporal Lobe

Challenges to the Dorsal–Ventral Stream Dichotomy

Summary

A fun-loving, middle-aged woman, C.J., had spent her entire adult life as an outdoor enthusiast. Then she suffered a mild stroke that damaged a small portion of the posterior section of her right hemisphere. She hated the confinement of the hospital and eagerly awaited her chance to spend some time outdoors again. Because her basic visual processing abilities were intact (an indication that the lesion had spared primary and secondary visual areas), she didn't anticipate having any problems doing the things she loved: hiking, skiing, and backpacking.

A few weekends after being released from the rehabilitation unit, C.J., along with her friend Sarah, decided to take a day hike up to a mountain pass. They started up the trail on a beautiful, crisp autumn day, with great views of the valleys below unfolding behind them. They hiked for about an hour, passing a number of turnoffs, until they entered a more forested area, where the trail became less well defined and had many switchbacks. The hiking was difficult, but C.J. was feeling like her old self again. Soon afterward, they came to a fork in the trail. They knew from the map that their cutoff should be nearby, but they weren't sure exactly where, so C.J. decided to pull out the map and compass. Once she had them out, though, she had difficulty determining how to align the map with reference to the compass. As she had previously had a strong sense of direction, C.J. was surprised to find herself confused as to which way was north, east, south, or west. At that point, Sarah called out, saying that she had found a

trail marker indicating that they wanted the rightward fork. C.J. was relieved to realize that despite her trouble with the map and compass, she had no trouble correctly distinguishing the rightward fork of the trail from the leftward one.

They reached the top of the pass after a couple of hours and were rewarded with a spectacular view of mountains all around them. As was their usual routine, they pulled out their map and tried to identify the surrounding peaks. Even though both the compass and the position of the sun could be used for orienting their direction, C.J. once again found herself confused. She was unable to translate the fantastic vista in front of her to the representations on the map. Although she and Sarah usually disagreed about the position of at least one mountain (after which a lively discussion would ensue), this time C.J. just listened carefully, startled at her own confusion.

C.J. was subdued on the hike down. Usually fit, she was a bit out of shape from her hospital stay, and as with any trauma, her body had not yet fully recovered. Sarah asked C.J. whether she was feeling okay, and although C.J. said that she was just tired, her mind was elsewhere. She was wondering whether her stroke might have had some unexpected consequences that would interfere with one of her favorite pastimes.

The story about C.J. helps to illustrate that spatial processing is not a simple cognitive function, but rather consists of many different abilities. Some of C.J.'s spatial abilities, such as understanding the relationship between the map and the surrounding terrain, and knowing geographical points of reference (north, south, east, and west), were compromised by her stroke, yet other abilities – such as determining left and right – were unaffected. In this chapter, we examine the many ways in which spatial relations among items can be computed and the brain systems that underlie and enable these computations.

We learned in [Chapter 5](#) that the visual cortex provides a precise retinotopic map of space. However, a retinotopic map is inadequate for fully understanding the space around us. First, as we have already discussed in relation to object recognition, the retina only provides two-dimensional information about the three-dimensional world. Second, you need to create a mental map of space that is constant regardless of where your eyes are looking, where your head has turned, and which way your body is facing. For example, you need to know that the cup of coffee sitting on the table just to the left of your hand is the same cup of coffee, both when it is in the center of your retinotopic map (as when you are looking directly at it) and when it is slightly off center in your retinotopic map (as when you move your eyes to the piece of cake sitting next to it).

Third, retinotopic maps provide information only about the scene as you are currently viewing it. Often, however, we need a mental representation of space that includes areas that we are not currently viewing. For example, when you turn your head away from the table to greet a friend who is joining you for coffee, you need to remember the position of that full cup of coffee so that you don't knock it over when you get up to shake hands. Finally, you also need spatial maps that extend to places that aren't within your field of view. To be able to get from your house to the coffee shop where you will meet your friend, you need a mental map of the larger world around you.

This chapter discusses several major issues related to the brain's processing of space. After a general overview of the dorsal visual system, we consider how the brain is able to code for the three dimensions of space, including issues in coding for left and right and calculating depth. Next, we consider how the brain is able to consider spatial relations with respect to different reference frames, such as an object's position relative to your eye position or the position of another object. Our discussion then extends to the topic of motion. The perception of motion is closely tied to spatial perception, because motion is inferred from the change in an object's spatial position over time. We then consider the relationship between spatial understanding and action. After all, it's no good knowing where that cup of coffee is located unless you can reach out and grab it.

And, finally, we explore spatial navigation, the set of skills that allows you to easily find your way to the neighborhood coffee shop.

An important emergent theme is that space is coded to serve multiple different functions, and these functions rely upon overlapping streams of information processing in the dorsal stream (primarily in the parietal cortex) and closely connected brain areas. Representing an object's location in three dimensions, with reference to the eyes, body, or external reference point, as well as its trajectory moving through space, for purposes of orienting the eyes toward it, reaching toward it, grasping it, or moving around or through it – these functions cannot all be addressed through a simple computation or single path of processing. Rather, interacting networks arising from V1 origins but extending throughout parietal cortex and beyond are critical for allowing us to engage in all the aspects of spatial cognition that are critical for successful interaction with the world around us.

The Dorsal Visual System for Spatial Cognition

In [Chapter 6](#), we examined the functioning of the ventral visual processing stream, which plays an important role in object recognition. In this chapter, we focus on the dorsal visual processing stream. This processing stream projects from primary visual areas to parietal regions, and it supports many aspects of spatial processing. The main components of the dorsal stream are shown in [Figure 7.1](#).

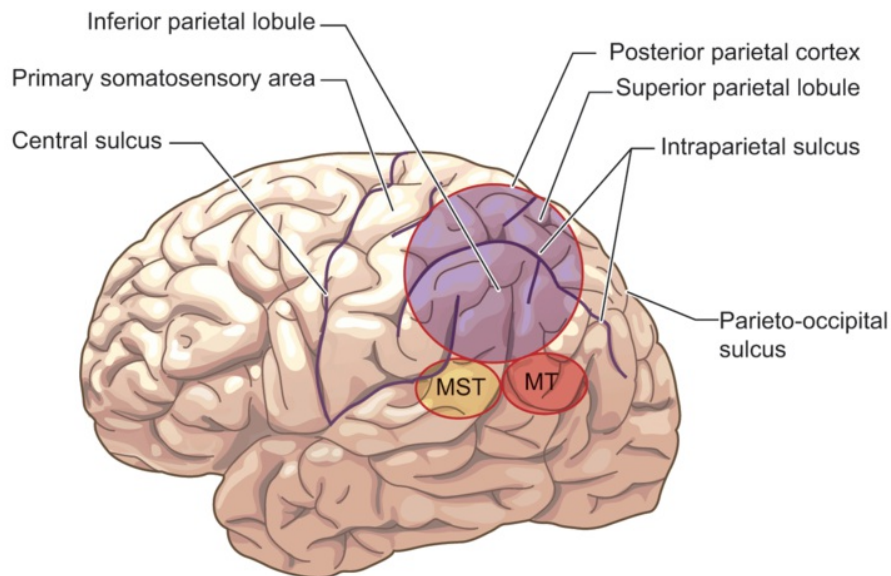


Figure 7.1 Dorsal visual stream.

Major dorsal stream areas are shown in the human brain. The parietal lobe is separated from the frontal lobe by the central sulcus and from the occipital lobe by the parieto-occipital sulcus. The primary somatosensory cortex, in the anterior parietal lobe, is not part of the dorsal stream proper. The posterior parietal lobe is divided by the intraparietal sulcus into the superior parietal lobule and the inferior parietal lobule. Finally, temporal lobe areas MT and MST are important for motion perception.

Anatomy of the Dorsal Stream

As you can see, many key components of the dorsal stream are located in the parietal cortex, which has several subdivisions. The anterior parietal lobe is concerned primarily with somatosensory representations, and is not considered part of the dorsal stream proper. In contrast, the posterior parietal cortex (PPC) is multisensory and is crucial in many aspects of spatial cognition. Within the PPC, researchers often distinguish between the superior parietal lobule and the inferior parietal lobule, which are separated by the intraparietal sulcus. In cortex buried within the intraparietal sulcus, different subregions have been distinguished that appear to be important for visual guidance of specific kinds of actions, as we will learn later. In addition to these parietal areas, other cortical regions are also relevant to the dorsal stream. For example, areas

MT and MST (the medial superior temporal area) contribute to our understanding of motion.

The dorsal stream is well positioned to subserve spatial functions. The dorsal stream receives visual information from the primary visual cortex, and it also receives input from the somatosensory cortex in the anterior parietal lobe and from the vestibular system, both of which provide information about the position of the body in space. This convergence of information from different senses allows regions of the parietal lobe to construct a multisensory representation of space in reference to the body's position.

Three separate pathways project from the dorsal stream to other brain regions to support different spatial functions ([Figure 7.2](#); Kravitz et al., [2011](#)). The first output path connects parietal cortex with prefrontal cortex, and is primarily concerned with supporting spatial working memory (which we will revisit in [Chapter 9](#), which focuses on memory). The second path connects parietal cortex with premotor cortex, and is primarily concerned with supporting visually guided actions such as reaching and grasping (discussed later in this chapter). Finally, the third path connects parietal cortex with medial temporal cortex (including hippocampus and parahippocampal cortex) and is concerned primarily with supporting spatial navigation, such as wayfinding around an environment (also discussed later in this chapter). This three-path model underscores the diverse spatial functions supported by parietal cortex in conjunction with other brain regions.

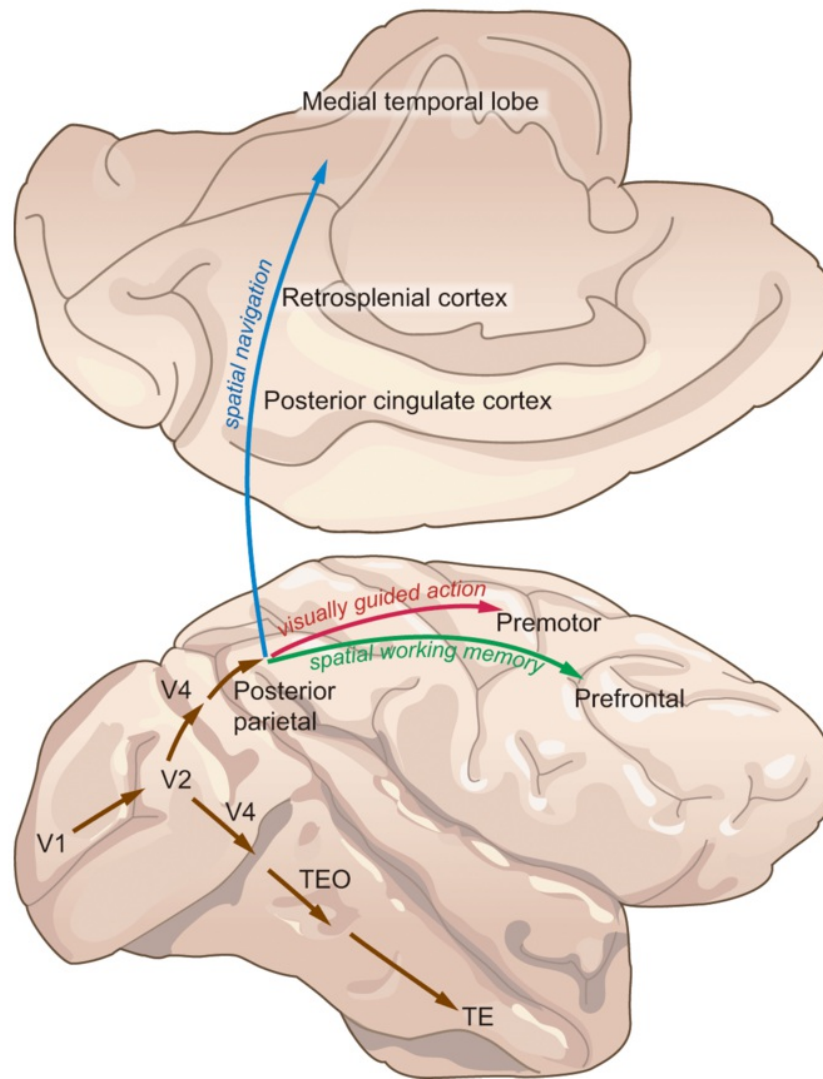


Figure 7.2 Three anatomical paths projecting from parietal cortex.

The path from parietal to prefrontal cortex (green) is thought to be important for spatial working memory. The path from parietal to premotor cortex (red) is thought to be important for visually guided action. Finally, the path from parietal to medial temporal regions (blue; via the posterior cingulate cortex, and retrosplenial cortex) is thought to be important for spatial navigation.

(from Kravitz et al., [2011](#))

Cellular Properties in the Dorsal Stream

Just as the properties of cells in the ventral visual system make those cells well suited for the task of object recognition, so properties of cells in the dorsal stream make the

cells well suited to process spatial information (for review, see Rozzi et al., [2008](#); for classic studies, see Andersen and Mountcastle, [1983](#); Motter and Mountcastle, [1981](#)). Research with monkeys indicates that posterior parietal cells are sensitive to different attributes than cells in temporal regions. Unlike cells in the ventral processing stream, cells in parietal areas are not particularly sensitive to form or color, making them ill-suited for detecting the visual properties from which shape can be derived. Furthermore, they are not particularly sensitive to items positioned in central vision, where acuity is the highest, a fact indicating that these cells do not play a large role in object recognition.

Cells in the posterior parietal cortex are most responsive to attributes of visual information that are useful for processing spatial relations. First, cells in this area appear to be responsive to a combination of the retinal location of the visual stimulus and the position of the animal's eyes or head, which allows the creation of a stable spatial map of the world. Second, the cells seem to fire in response to a specific direction of motion, either inward toward the center of the visual field or outward toward the periphery. Such sensitivity provides a means for objects to be tracked as they move across space. Third, the optimal velocity of movement for stimulating these cells to fire is about the speed at which the animal walks or runs. Sensitivity to this range of speeds provides a way to update the spatial positions of items as the animal moves past them while locomoting. Finally, cells within the inferior parietal lobe often fire in close relationship with planned movements such as reaching or grasping, as well as in response to visual and tactile stimuli. These joint sensory-motor cells reflect the close relationship between spatial perception and action within the dorsal stream.

Coding for the Three Dimensions of Space

Space, as you know, is three-dimensional. This might seem like stating the obvious, but it is worth thinking about how the brain is able to code for the three dimensions of space: namely, the vertical (up-down) dimension, the horizontal (left-right) dimension,

and the depth (near-far) dimension. As discussed in [Chapter 5](#), the retinal images that the brain receives are two-dimensional, and the depth dimension must be computed in the cortex. We begin by discussing the coding of spatial dimensions that can be derived directly from the retinal image, and then turn to coding of depth.

Distinguishing Left From Right

As we learned in [Chapter 5](#), the visual world is mapped in a retinotopic manner onto visual cortex, with the map reversed in relation to the visual world with respect to both the up-down and left-right dimensions. It would seem fairly easy to distinguish left from right based on this map-like organization within the brain's visual processing stream. However, it is trickier to distinguish left from right than to distinguish up from down, the other dimension coded on the retina. Developmentally, children often confuse left and right long after they have a clear understanding of up and down. One study even found that a sizable minority of college professors report having some left-right confusion (Harris and Gitterman, [1978](#)). What is so hard about telling left from right? Whereas up and down can be easily determined with respect to an absolute reference point (the earth), left and right are inherently relative terms. For example, if I am facing you, an object on my right side is on your left side, and vice versa.

A fascinating patient described by Michael McCloskey and colleagues ([1995](#)) demonstrated vividly how left-right understanding can go wrong. The patient, a college student with no known brain damage, had a history of trouble with reading, but her problems turned out to be more pervasive. Numerous tests showed that she often mistakenly perceived the spatial locations of items in a mirror-image fashion. [Figure 7.3](#) dramatically illustrates what happened when the patient was asked to directly copy a complex figure. Notice how many of the figure's elements she places in the opposite location across the left-right midline. The patient also showed mirror-reflections in a simple reaching task. A target would be placed in a particular position – say, 45 degrees to the left of midline – but the patient would initially reach for it in the location 45

degrees to the right of midline. The fact that the patient's reaching was not random, but rather mirror-reversed, suggests that she was able to represent some aspects of the object's spatial coordinates correctly. However, she consistently misrepresented the object's direction in the left-right dimension.

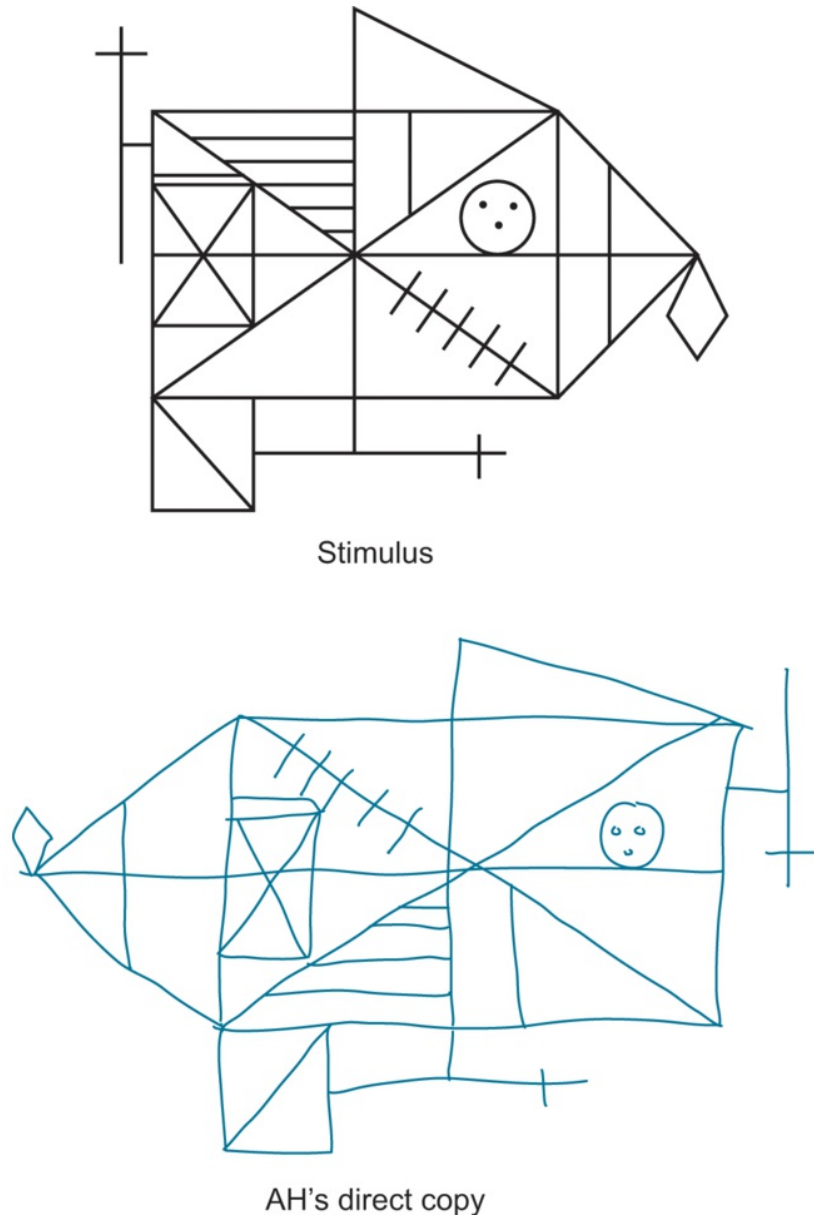


Figure 7.3 Evidence of left-right mirror reflection in a patient.

The patient's direct copy of the complex stimulus figure is shown at the bottom.

Source: Figure 1 from McCloskey, M., et al. (1995). A developmental deficit in localizing objects from vision. *Psychological Science*, 6, 112-117. Reprinted by permission of Association for Psychological Science.

Studies of other patients confirm that spatial coding of right and left can be independently disrupted. For example, one patient with localized brain damage in the right occipitoparietal region demonstrated difficulty distinguishing between objects based on their left-right orientation (Martinaud et al., 2014). When this patient viewed

stimuli such as that shown in [Figure 7.4](#), in which one member of an array was mirror-reversed in the horizontal (left-right) plane, she was deficient at picking out the item that was different from the others. The patient performed normally when the target item was mirrored in the vertical (up-down) plane, or when it was presented in a different orientation, such as rotated 90 degrees in the plane of the page rather than mirror-reversed. In other words, it was understanding of left-right mirror-imaging specifically, rather than changes in spatial representation more generally, that was deficient in the patient. The patient also performed normally in selecting the target item when it differed in shape compared to the other items, indicating no problem with object shape perception. The fact that her lesion was localized to the boundary between occipital and parietal cortex fits with the notion that the left-right aspect of spatial coding is implemented by the dorsal stream.

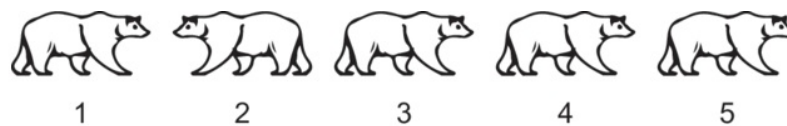


Figure 7.4 Task assessing left-right orientation in brain-damaged patients.

The patient is asked to indicate which of the items is different than the others. A patient reported by Martinaud et al. ([2014](#)) had difficulty identifying mirror-reversed targets as different, even though she performed the task normally if the target item was instead rotated in the plane of the page (e.g., clockwise or counterclockwise), reversed along the vertical (up-down) axis, or differed in shape from the rest of the array.

Depth Perception

Depth perception helps us to localize items in the near-far plane. As discussed in [Chapter 5](#), depth is not provided directly by the retinotopic map, but it can be computed in part by comparing the images from the two eyes. The amount of [binocular disparity](#), or discrepancy between the images seen by the two eyes, is a cue to depth. Cells in

primary visual cortex are sensitive to different amounts of binocular disparity, and provide important information about depth for use by the dorsal stream regions.

Depth perception is crucial to an understanding of space, and therefore we would expect the dorsal stream to code for depth information in some way. Studies with other primates have established that cells in various regions of the dorsal stream are sensitive to binocular disparity (see Parker et al., [2016](#); Roe et al., [2007](#), for reviews). In these areas, different subsets of cells are most responsive when the eyes are fixated at different locations in depth, much the way that certain cells in the ventral visual stream seem to be tuned to specific objects. Most of these cells respond maximally when the eyes are fixated on locations in near space, but others prefer locations in far space.

Another important cue to depth, besides binocular disparity, is motion parallax. Motion parallax refers to the fact that as you move through an environment, near objects are displaced more on your retina than objects that are far away. For example, as you look out a car window while driving, the signs on the highway whiz by quickly, whereas the mountains in the distance remain more stable. Motion parallax is a monocular depth cue, meaning that it can be perceived based on input from only one eye (in contrast to binocular disparity). Recent evidence from single-cell recordings in monkeys indicates that cells in area MT (which we discuss in more detail later in the section on motion perception) are responsive to depth cues in both the form of binocular disparity cues and the form of motion parallax cues (Nadler et al., [2013](#)). In other words, these cells appear to integrate different kinds of cues (binocular disparity and motion parallax) to code for depth.

These studies indicate that individual cells are sensitive to depth information, but how do we know that these cells actually are responsible for the perception of depth? One study addressed this issue by stimulating clusters of cells sensitive to binocular disparity within area MT and observing the effect on monkeys' perceptions (DeAngelis et al., [1998](#); see also Uka and DeAngelis, [2006](#)). In the experiment, monkeys had to indicate the depth of a stimulus through either an up or down eye movement (up for far stimulus, down for near stimulus). The researchers found that when near-preferring cells

in area MT were stimulated, the monkey's eye movements indicated that it was seeing the stimulus at a near depth location; likewise, when far-preferring cells were stimulated, the monkey's eye movements were biased toward far target locations. This study demonstrates that activity of MT cells influences the monkey's perception of depth.

Evidence from humans suggests that although damage to the parietal cortex in humans can impair depth perception (e.g., Holmes and Horax, [1919](#)), there does not seem to be any syndrome in which perception of spatial depth is disrupted but all other spatial functions are intact. This finding tells us that coding for depth probably does not rely upon a single dedicated brain region whose function is to compute depth and nothing else. Rather, processing of depth probably occurs throughout various dorsal stream areas that represent space for a variety of purposes, such as providing a spatial framework for reaching and grasping motions and for understanding motion in the plane of depth. This idea is consistent with the finding that cells across many regions in the dorsal stream of monkeys show sensitivity to depth.

Spatial Frames of Reference

One important aspect of coding spatial information involves [frames of reference](#). This concept refers to the idea that we can understand the spatial location of an object with respect to multiple reference points. For example, imagine that you are sitting at a table with a bowl of fruit in front of you. Your body is aligned with the bowl of fruit, but your head is tilted slightly to the left as you turn your eyes to the right to gaze at a person standing beside the table. Consider now the task of representing where that fruit bowl is located. First, imagine where the bowl is in relation to your body midline; it is directly in front of the midline of the trunk of your body. However, because your head is tilted, the bowl is not neatly lined up with the midline of your head. Also, because your eyes are shifted rightward within your head, the bowl is not falling on the midline of your retina, either. In other words, because the trunk, head, and eyes can all move

independently, an object's location relative to any one of these body parts must be coded independently. At the same time, these reference frames also have to be co-referenced to one another to provide a stable representation.

The frames of reference we just mentioned – body-centered, head-centered, and eye-centered – all belong to a category of reference frames known as [egocentric reference frames](#) because they all specify an object's location in relation to some aspect of the self. However, we can also think of spatial relations in ways that do not specifically refer to the self. For example, you could consider whether the fruit bowl is on top of or underneath a book, or you could specify how many inches the bowl is from the salt shaker. When you consider spatial relations of objects relative to one another, and independent of your own location, you are specifying the object locations in an [allocentric reference frame](#).

Neural Coding of Reference Frames

Studies using single-cell recordings in monkeys have begun to reveal how multiple frames of reference are coded by the brain. To address this issue, first consider how receptive fields are mapped at the level of primary visual cortex. As we learned in [Chapter 5](#), individual cells in primary visual cortex have retinotopically defined receptive fields; that is, the cell will fire best when a particular location on the retina is stimulated with light. Now, consider a receptive field that is defined relative to the midline of the animal's head, regardless of where the eyes are looking. A cell with a head-centered receptive field would fire optimally when a visual stimulus appears a certain distance from the midline of the head, even if the animal's eyes are fixated off to the side rather than aligned with the midline of the head (see [Figure 7.5](#)). Cells with head-centered receptive fields code for space in a more complex manner than cells in primary visual cortex. Such cells must compute a head-centered location based on combining two sources of information: the place on the retina that was stimulated and the position of the retina in relationship to the head midline. While both types of coding

– retinotopic (eye-centered) and head-centered– involve egocentric reference frames, they are nonetheless distinct.

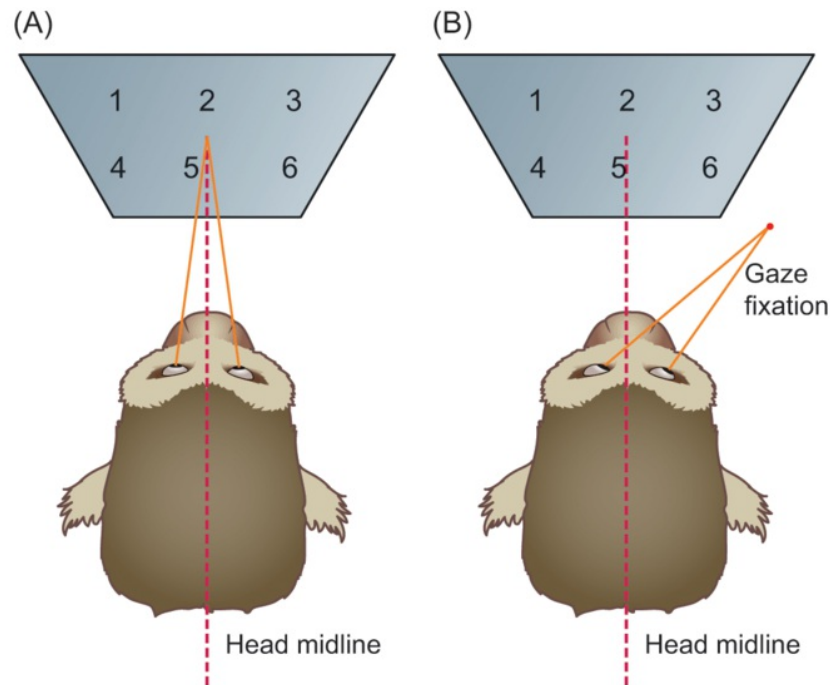


Figure 7.5 Illustration of head-centered coding of spatial location.

Head-centered cells have receptive fields that are defined in relation to the head midline. Imagine recording the activity of a single cell as a monkey views a screen on which a light could flash in one of six locations (numbered 1–6 in the figure). Consider a head-centered cell that fires strongly when the light flashes at location 1 in panel A, but does not respond when the light flashes at locations 2–6. When the monkey shifts its eyes rightward, as in panel B, this head-centered cell will continue to fire most strongly to light at location 1, even though that stimulus is now striking a different part of the retina. As long as the head remains in the same position, this head-centered cell will continue to fire to light in location 1. A cell that coded for space in allocentric terms would continue to fire to its preferred location (such as location 1) even if the monkey moved its head or body.

One study investigated whether cells in the parietal cortex are more sensitive to head-centered or eye-centered (retinotopic) spatial location (Mullette-Gillman et al., [2005](#)). Approximately 33% of visually responsive cells in the subregions sampled,

including lateral and medial intraparietal cortex (see [Figure 7.6](#)), coded for location primarily in eye-centered (retinotopic) coordinates, about 18% of cells coded primarily for head-centered coordinates, and the remainder of the cells (nearly half) could not be easily categorized as either solely head-centered or solely eye-centered. Thus, it seems that different kinds of egocentric representations (head-centered versus eye-centered) are coded by overlapping populations of cells.

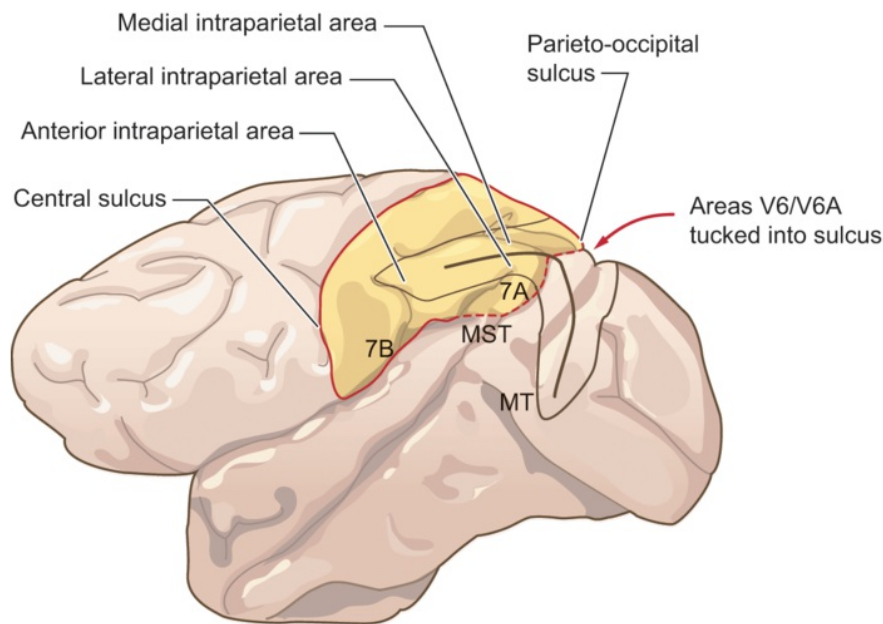


Figure 7.6 Subregions of posterior parietal cortex in macaque brain.

Single-cell recordings have found that cells in medial and lateral intraparietal cortex tend to code space in either eye-centered or head-centered frames of reference, whereas cells in area 7A tend to code space in allocentric (object-centered) frames. Cells in areas V6 and V6A encode information about eye position, which aids in the interpretation of spatial information.

In order to calculate an object's location in a head-centered frame of reference (rather than eye-centered frame of reference), the parietal cortex needs to take into account both the retinotopic image and the position of the eyes in relation to the head. In other words, gaze direction must be encoded in order for the parietal cortex to compute head-centered representations. Single-cell studies confirm that information about eye position is encoded in posterior parietal cortex, in regions such as areas V6 and V6A,

which are tucked into the parieto-occipital sulcus (see [Figure 7.6](#); Andersen and Mountcastle, [1983](#); Nakamura et al., [1999](#); see also Breveglieri et al., [2012](#); Hadjidimitrakis et al., [2014](#)).

Allocentric representations appear to be coded in different subregions of the parietal lobe than egocentric representations such as eye-centered and head-centered representations. Cells within one subregion (the lateral intraparietal region, LIP; see [Figure 7.6](#)) are sensitive to spatial location in egocentric coordinates but not sensitive to spatial location in allocentric coordinates. Conversely, cells in another subregion (area 7A) tend to be more sensitive to allocentric coordinates (Snyder et al., [1998](#)).

These two kinds of reference frames (allocentric and egocentric) may be important for different functions. Specifying an object's location in relationship to the eyes can be helpful in controlling gaze direction; for example, knowing how far to shift the eyes to look directly at that object. Consistent with that hypothesis, the LIP region is anatomically connected with brain regions that control eye movements, such as the frontal eye fields. In contrast, allocentric coding is more important for navigating through a spatial environment, in which we must understand how objects and landmarks are related to one another. Therefore, area 7A, which has more allocentrically sensitive cells, projects to regions of the brain that are important in navigation, such as the parahippocampal gyrus.

One puzzle is how the brain is able to compute allocentric frames of reference, when the initial input coming into the dorsal stream is represented in a retinotopic (eye-centered) frame of reference. One group of researchers had monkeys complete a task in which they viewed a target object with one piece missing and had to identify the location of the piece that would complete the object correctly (Crowe et al., [2008](#)). The researchers recorded the firing of 20–30 individual neurons in a region within the superior parietal lobe. During each trial of the task, this group of cells first coded information about the missing square's location in retinotopic coordinates (relative to the monkey's fixation point), and then about 100 ms later the same group of cells

represented the location of the missing piece in object-centered coordinates (relative to the center of the object, independent of where the monkey's gaze was fixated). Thus, this ensemble of cells seems able to compute the necessary transformation of spatial information from a retinotopic to an allocentric reference frame. Researchers are still attempting to understand exactly what inputs the cells use to engage in this computation and how they transform the information from one reference frame to another.

Adding to the complexity, the parietal cortex is also involved in creating representations of space that are multisensory; that is, based on senses such as touch and hearing as well as vision. However, information from touch and audition is not necessarily represented in the same frame of reference as visual information. For example, eye-centered representations are more likely for vision than for other senses, whereas head-centered coordinates are more likely for touch and audition. How, then, is spatial information from multiple senses integrated? One possibility is that regions of the parietal lobe manage to align maps constructed from different senses. Single-cell recording studies in monkeys suggest that in some areas of the parietal cortex, such as a ventral region of the intraparietal area, the same cells represent tactile information in a head-centered reference frame and visual information in either head-centered or eye-centered reference frames (Avillac et al., [2005](#)).

As you can see, researchers are still far from understanding exactly how multiple reference frames from various senses are coded and integrated. However, single-cell recordings from monkeys point to some general conclusions. First, the spatial representations encoded in posterior parietal cortex are abstracted beyond the simple retinotopic (eye-centered) representations in primary visual cortex. Some parietal cells code for space in head-centered or object-centered frames. Second, different subpopulations of posterior parietal cells participate in coding space for different functions. For example, eye-centered or head-centered representations may be critical for exploring the visual environment with the eyes (i.e., through eye movements), while allocentric representations are more critical for moving the body through the

environment. Third, coding of location is a dynamic process that must constantly take into account the changing position of the eyes.

Dissociability of Reference Frames

Studies of brain-damaged patients indicate that different reference frames can be independently disrupted by brain damage. That is, in a given patient, spatial understanding in one frame of reference may be affected while other frames of reference are spared. The best evidence for this conclusion comes from studies of patients with hemineglect, in whom damage to the right hemisphere produces a failure to attend to the “left” side of space (see [Chapter 10](#) for fuller discussion). Some hemineglect patients fail to attend to information on the left side of the body midline, whereas others fail to attend to information on the left side of the head. Some patients may even neglect the left-hand side of an object regardless of where that object is placed in relation to the patient’s body, indicating an object-centered form of neglect (for reviews, see Corbetta and Shulman, [2011](#); Halligan et al., [2003](#)).

Does disruption of different frames of reference in different hemineglect patients result from different anatomical areas of damage? If so, perhaps we could gain a clearer sense of whether certain anatomical regions are critical in supporting spatial cognition in certain reference frames. Some evidence indicates that egocentric neglect is most often associated with damage to the right parietal lobe, whereas [object-centered neglect](#) is most often seen in conjunction with damage to middle and inferior temporal lobe regions in the right hemisphere (Medina et al., [2009](#); see also Verdon et al., [2010](#)). The association of object-centered neglect with ventral rather than dorsal stream regions fits with the role that the ventral stream plays in coding for object shapes.

Evidence from patients with neglect also tells us that space can be divided into different realms or spheres based on distance relative to the body (Committeri et al., [2007](#); di Pellegrino and Làdavas, [2015](#)) (see [Figure 7.7](#)). Personal space refers to spatial position on the body. For example, some neglect patients show left-sided neglect only with respect to their own bodies, such as failing to shave the left side of the face.

Other neglect patients show neglect only for the left side of peripersonal space, which refers to the spatial realm within arm's reach, or near space. Finally, there are also neglect patients who seem to have the most trouble with information presented on the left side beyond arm's reach, in what is referred to as extrapersonal space or far space. Because patients' understanding of space can be independently disrupted in either the personal, peripersonal, or extrapersonal realms, it seems that these regions of space must be coded using somewhat different brain regions or processes.

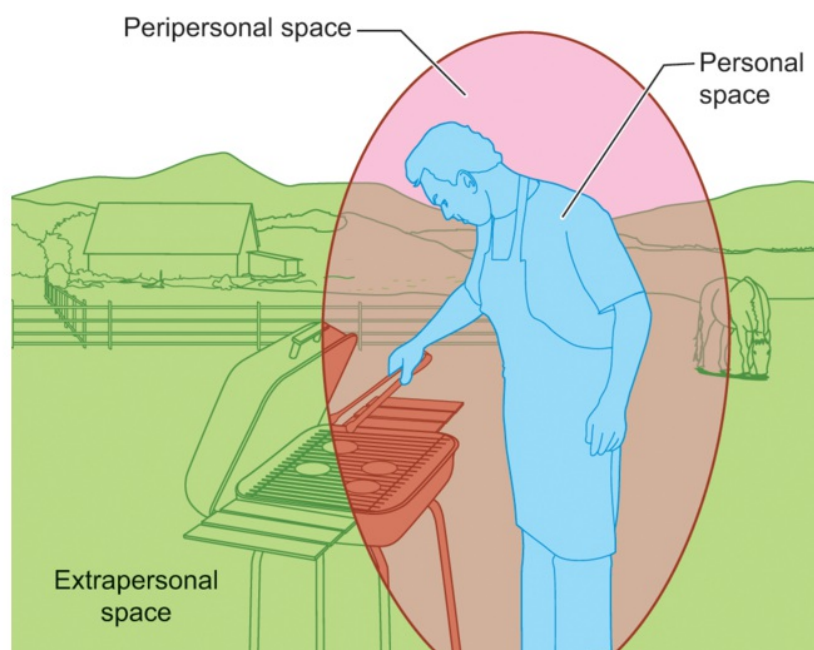


Figure 7.7 Illustration of personal, peripersonal, and extrapersonal realms of space.

Studies of patients with hemispatial neglect have found that coding for these different realms of space can be independently disrupted by brain damage.

Categorical Versus Coordinate Spatial Relations

An important aspect of spatial relations is representing where objects are located in relationship to one another. Consider a scene in which you are eating dinner with a friend. You want to be able to locate a particular item, such as a bowl of mashed potatoes, but you also want to be able to understand its relationship to the other items on

the table. For example, if your friend is looking for the salt, you might tell her that “The salt is behind the bowl of mashed potatoes.” Or, you might notice that the salt is a couple of inches past her grasp, and so you pass it to her.

These examples illustrate the difference between categorical and coordinate spatial relationships. The spatial relationship described in the first example (the salt is behind the potatoes) is an example of [categorical spatial relations](#), which specify the position of one location relative to another in dichotomous categorical terms (e.g., above versus below, top versus bottom, front versus back, left versus right). The spatial relationship described in the second example (the salt is two inches beyond a person’s grasp) is an example of [coordinate \(or metric\) spatial relations](#), which specify the distance between two locations. Metric and categorical spatial relations are considered to be independent of one another, because describing the distance between two points from a metric perspective (e.g., 3 inches apart) doesn’t necessarily provide information about their relationship from a categorical perspective, and vice versa.

Several lines of evidence indicate that categorical and coordinate spatial relations are represented independently in the brain, with the left and right parietal regions implicated in the two types of relations, respectively (e.g., Kosslyn, [2006](#); van der Ham et al., [2014](#)). For example, people typically perform better in making categorical judgments in the right visual field (processed by the left hemisphere) and coordinate judgments in the left visual field (processed by the right hemisphere) (see [Figure 7.8](#) for examples). Brain imaging and TMS studies also confirm this hemispheric distinction for categorical and coordinate spatial relations (Slotnick and Moo, [2006](#); Trojano et al., [2006](#)).

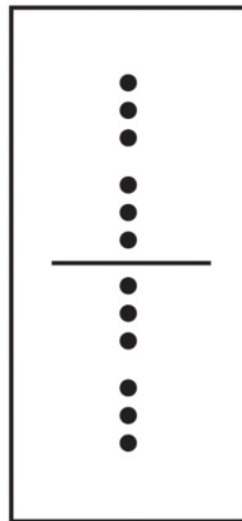
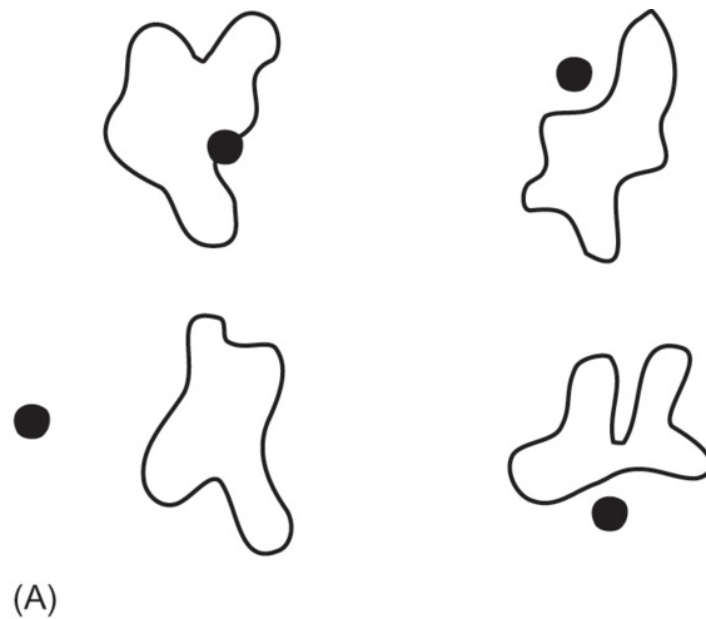


Figure 7.8 Examples of stimuli used to investigate the difference between categorical and metric spatial relations.

(A) Each of these four stimuli is shown individually. In the categorical task, an individual is asked to decide whether the dot is on or off the blob. In the metric task, the person is asked to decide whether the dot is near or far from the blob. (B) In this task, the bar and one dot are shown in each trial. The figure depicts 12 possible locations of dots. In the categorical task, subjects decide whether the dot was above or below the bar. In the metric task, they decide whether the line is near (within 0.79 in., or 2 cm) or far away (further than 0.79 in., or 2 cm) from the dot.

Recent evidence also indicates that these two forms of understanding spatial relations are associated with differences in the scope of spatial attention. For example, in one study, participants were cued to pay attention to either a small or large region of space, and then had to make either a categorical judgment about a stimulus (whether it matched the sample in categorical relations between two items) or a coordinate judgment about the stimulus (whether it matched the sample in metric distance between two items). Using MEG, the researchers found that large cues paired with coordinate judgments differentially activated the right inferior parietal lobe, whereas small cues paired with categorical judgments differentially activated the left inferior parietal lobe (Franciotti et al., [2013](#); see also van der Ham et al., [2012](#)). Thus, hemispheric differences in processing spatial relations appeared to be linked to hemispheric differences in attending to large versus small regions of space.

In sum, research discussed in this section should give us an appreciation for the many different ways in which spatial location can be coded. Location can be specified in relationship to the eyes (retinotopic mapping), the head (head-centered representation), or some external reference point (allocentric coding) such as the object itself. Location may also be considered in terms of the body (personal space), peripersonal space, or extrapersonal space. Finally, spatial relations between two objects can be coded either in categorical (dichotomous) or coordinate (metric) terms. Different subpopulations throughout the parietal cortex appear to participate in these different forms of spatial coding.

Motion Perception

So far we have considered a spatial world in which spatial relations are static. But spatial relations can change with time; that is, they often involve motion. Motion perception is inherently tied to spatial perception, because perceiving motion involves perceiving changes in an object's spatial location over time. In addition, we must be

able to represent our own motion through the world in order to fully understand where we are presently located.

Specific Neural Regions for Motion Perception

A clinical case study provides some initial evidence that the analysis of motion has a unique neural substrate, different from that which supports other spatial skills. The patient in this study lost her ability to perceive motion in all three dimensions, but her other basic visual and spatial functions were intact, including visual acuity, binocular vision, color discrimination, discrimination of visual objects and words, and localization of items in space (Zihl et al., [1983](#)). As you might imagine, this disorder created much difficulty in her life. When pouring liquids, such as tea or coffee, the flowing stream would appear to this patient as a glacier or a snapshot, much the way such a stream does in magazine ads. Because she could not see the rising level of fluid in a container, it was impossible for her to determine when to stop pouring. Even more troublesome was her difficulty in judging the speed of cars (which she had no trouble recognizing). This impairment made crossing streets extremely dangerous. In describing her dilemma, she said, “When I’m looking at the car, first it seems far away. But then, when I want to cross the road, suddenly the car is very near” (Zihl et al., [1983](#), p. 315). Eventually, she learned to rely on auditory cues, such as the loudness of a car, to estimate how close or far away it was.

A vast amount of research in both monkeys and humans has more specifically identified the brain regions that are crucial to the ability to perceive and represent motion (Orban and Jastorff, [2014](#); Zeki, [2015](#)). The two most important regions are areas MT (also known as V5) and MST (look back on [Figures 7.1](#) and [7.6](#)). **Area MT** receives input from early visual areas like V1, V2, and V3, and it sends projections back to those areas as well as to higher-level areas like the ventral intraparietal cortex and area MST. In the monkey, area MT gets its name from its location, in the middle temporal lobe. In humans, the exact location of the area referred to as MT is somewhat

more variable, but it is still called MT because its function parallels that of monkey MT (e.g., Bridge et al., [2014](#); Large et al., [2016](#)).

Single-cell studies in monkeys suggest that activity in area MT leads to the perception of motion. First, single cells in area MT respond best to a pattern that moves in a particular direction and with a particular speed, with different cells having different speed and directional preferences (Born and Bradley, [2005](#); Zeki, [1974](#)). Researchers found that the firing rate of certain speed-preferring MT cells could actually predict a monkey's behavioral response in a task that required indicating which of two patterns was moving faster (Liu and Newsome, [2005](#)). Cells in area MT can represent motion not only along the two dimensions depicted directly on the retina (i.e., vertical and horizontal planes), but they can also represent motion in depth (e.g., movement toward or away from the viewer) (Czuba et al., [2014](#); Sanada and DeAngelis, [2014](#)).

Perhaps the most impressive evidence linking area MT with motion perception has come from experiments in which the experimenter stimulated different groups of MT cells, each of which has certain speed preferences. The researchers looked at the effect of such stimulation on a monkey's decision about the speed of a stimulus. Depending on the group of cells stimulated, the experimenter could change the monkey's response, presumably by altering the monkey's perception of the stimulus speed (Liu and Newsome, [2005](#)). Stimulation of specific direction-preferring cells in area MT can also change a monkey's decision about the direction of movement of a stimulus (Nichols and Newsome, [2002](#)).

Imaging studies have confirmed that MT and surrounding regions become very active when people are viewing moving patterns (e.g., Tootell et al., [1995](#); see also Hesselmann et al., [2008](#)). In addition, disruption of area MT – due to brain lesions, TMS, or electrical stimulation – affects the perception of motion and the ability to use motion cues to guide actions (e.g., Becker et al., [2013](#); Bosco et al., [2008](#); Schenk et al., [2005](#); Whitney et al., [2007](#)). Finally, disruption of activity in area MT via TMS affects

mental rotation performance, pointing to the importance of MT-based motion perception in supporting the ability to imagine the rotation of an object (Seurinck et al., [2011](#)).

Area MST, like area MT, is sensitive to motion, but it seems to encode somewhat more complex patterns of motion. Specifically, cells in area MST respond to patterns that include optic flow (Duffy, [2014](#)). **Optic flow** refers to the pattern of movement of images on your retina as you move actively through an environment (see [Figure 7.9](#)). For example, imagine that you are running through a field. As you run, the world is whipping past you; trees, shrubs, and fenceposts first appear before you, and then fly by as you pass them. The movement of these images on your retina forms a predictable pattern: the overall rate of movement will be determined by your running speed, and objects that are closer to you will appear to move past you faster than objects in the distance. In addition, objects get bigger as you approach them and then smaller after you run past them. You must be able to interpret this information to jump over a rock in your path at just the right time, or to know if your friend is about to overtake you in your dash across the field.

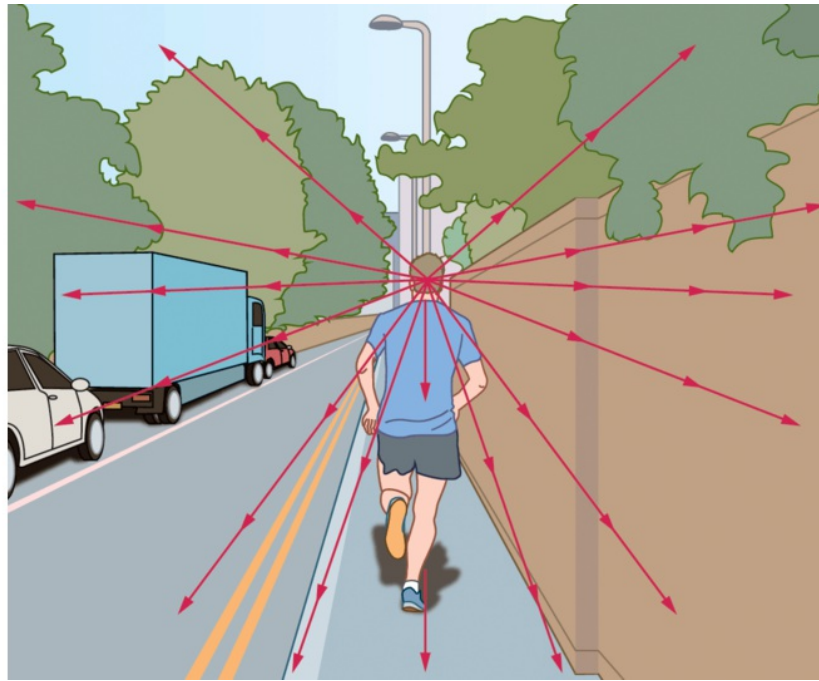


Figure 7.9 Example of an optic flow pattern.

As you move actively through your environment, you move past objects and scenes. The movement of the retinal image for each aspect of the scene (shown by arrows) will depend on your speed and direction as well as the spatial relationship of each scene element in relation to your body.

Although these kinds of flow patterns occur naturally all the time as we move through our environments, they can also be created in lab settings and characterized with mathematical precision. Numerous studies have found that cells in area MST are excited by optic flow bilaterally (in either visual field), whereas cells in area MT are most excited by simpler motion within the contralateral field only. We have here another example of the hierarchical nature of visual processing, as simple representations are built into more complex ones (see also Khawaja et al., [2013](#)).

Incorporating Knowledge of Self-Motion

One problem that the brain must solve is distinguishing between the real movement of an object in the world and the movement of an object's image on the retina. The position of an object's image on the retina can change for two reasons: either the object moved

while the retina remained in the same location, or the object remained stable while the retina moved because of an eye movement. For example, as illustrated in [Figure 7.10](#), the image of a car could appear to move across your retina either because the car is actually moving or because your eyes are scanning across the car while it is stationary. As you scan your eyes across a stationary object, such as a parked car, its image moves across your retina – yet you do not perceive the car to be moving. Why not? You can also think of the reverse situation, in which the image of a moving object remains stationary on your retina because your eyes are tracking it. For example, imagine that you are following a bird as it flies across the sky. If you are tracking it well, you will keep its image centered on your fovea, yet you still perceive it to be moving even though the retinal image is stable.

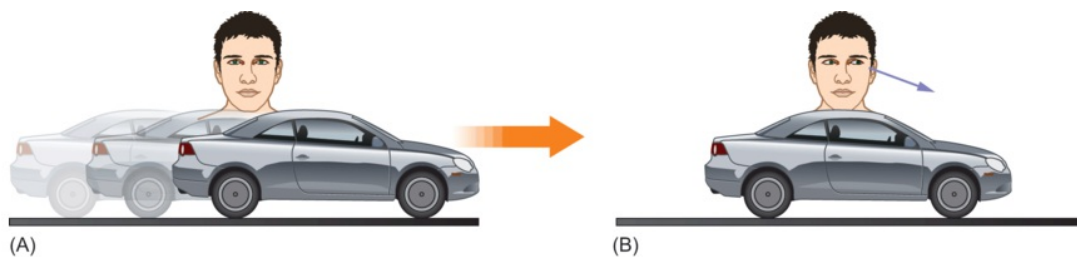


Figure 7.10 Two different conditions that can cause movement of a visual image on the retina.

(A) A person gazes straight out onto a street while a car drives by; the image of the car will move across the retina. (B) A person scans his eyes across a parked car. Here, the movement of his eyes will cause the image of the car to move across the retina.

Accounting for Movement of the Eyes

One way to illustrate the importance of distinguishing between object movement and retinal-image movement is to consider what happens when that ability is lost. Indeed, such a case has been reported in a patient with bilateral damage to extrastriate regions (Haarmeier et al., [1997](#)). The patient reported that when he moved his eyes across a stationary background pattern, the background pattern seemed to move. (Unfortunately,

this led to a lot of vertigo in his daily life.) To measure this phenomenon, the researchers determined how much movement of the pattern was necessary for it to seem stationary to the patient as he moved his eyes across it. They found that the patient perceived the pattern as stationary only when it was moving at the same speed as his eyes, and therefore when its image was kept stationary on his retina. (This is unlike the rest of us, who would perceive the pattern as stationary when it actually was stationary!) This patient had an impairment in incorporating information about his eye movements into his understanding of motion in the visual world.

How, then, can the brain distinguish real movement from movement of the image on the retina? The famous perceptual psychologist Hermann von Helmholtz proposed a solution to this problem back in [1910](#). Helmholtz understood that the only way to distinguish between real and retinal movement is if the movement perception areas of the brain receive information about eye movements. That is, if eye movements are taken into account, the visual system can figure out if the retinal image is moving because the eyes are moving or because the object itself is moving in the world. If the movement of the retinal image matches that of the eye movement, then the brain can infer that the object is really stationary. In contrast, if the movement of the retinal image does not match the eye movement, then the object in the real world must really be moving.

There are two different sources that could provide the visual system with information about eye movements, so that these eye movements can be taken into account in understanding the movement of a retinal image. One possibility is that the motor regions of the brain let the visual system know when they are planning to move the eyes; this is the model that Helmholtz proposed. According to Helmholtz's hypothesis, motor-planning regions of the brain send a [corollary discharge](#), which is a signal to visual areas about the upcoming eye movements. Although the precise neural mechanism corresponding to Helmholtz's corollary discharge signal has yet to be pinned down, anatomical pathways connecting the brainstem superior colliculus, frontal eye fields, and area MT provide a circuit by which eye-movement plans can be communicated with the motion perception area MT (Sommer and Wurtz, [2014](#)).

In addition, sensory receptors within the eye muscles provide ongoing feedback about changes in the position of the eye. Although sensory information about eye position may not be quite as useful as advance notice of upcoming eye movements from motor regions, such sensory feedback could provide additional information that is taken into account when the visual system interprets retinal-image motion. Supporting this possibility, cells within the somatosensory cortex of the monkey brain can represent the position of the eyes (Wang et al., [2007](#)).

A recent study using TMS in humans also found that the somatosensory cortex in the anterior parietal lobe encodes information about the position of the eyes. When the somatosensory cortex was transiently disrupted by TMS, participants were unable to correctly use cues from their eye positions to perceive what point was straight ahead of them (Balslev and Miall, [2008](#)). Because somatosensory cortex cells can code for the orientation of the eyes, they can provide useful information for motion-perceiving areas of the dorsal stream, as well as for processes that involve aligning eye-centered and head-centered frames of reference.

Accounting for Movement of the Body

Real-world motion perception is even more complex, because it is not only our eyes that can move, but our whole bodies. In fact, most of our perceptions probably occur while we are on the move, strolling through our neighborhoods or driving our cars around them. So, our motion perception systems must have a way of taking into account the whole body's movement through space (whether running, walking, or sitting in a moving car), to accurately perceive whether objects around us are moving or stationary.

Researchers are still determining how the brain is able to construct stable visual representations even as the body continuously moves through space. As mentioned earlier, it is known that area MST is especially responsive to visual motion in the form of optic flow, which is the pattern of visual-image movement formed by moving through a scene. In area MST and surrounding dorsal stream regions, these optic flow signals appear to converge with incoming information from the vestibular system. The

vestibular system provides sensory information from the inner ear about the body's movement (whether active or passive, as in a car) and body orientation with respect to gravitational forces. Area MST may then integrate information about the body's movement through space together with retinal-image information to infer the movement speed and direction of external objects.

Indeed, research indicates that area MST is important in an animal's ability to determine its heading. Heading here refers to the direction of forward motion of the body. (Imagine telling a friend "head north on Main Street" or "I'm heading down toward the park.") Monkeys, as well as people, are keenly able to perceive heading based on optic flow and vestibular cues, with acuity of about 1 degree of angle. Cells within MST in the monkey appear to code for heading direction (e.g., Bremmer et al., [2010](#); Britten and van Wezel, [1998](#); Gu et al., [2007](#)), and inactivation of MST interferes with the ability to distinguish different directions of heading (Gu et al., [2012](#)). Other dorsal stream regions (such as ventral intraparietal cortex and an area labeled V6) also contain cells that code for heading, and researchers are currently investigating the different functional roles these subregions may play in making use of heading information (Chen et al., [2011](#), [2016](#)).

The ability to know which direction you are heading is useful for many purposes. Our emphasis in this section has been on how understanding your own body's movement through space can help you to interpret the movement of images on your retina as you pass by different objects or scene elements. Additionally, knowing which way you are going is critical to navigation, an issue that we will return to in a later section.

Space and Action

Perception of spatial dimensions, reference frames, spatial relations, and motion is important in being able to construct an accurate view of the spatial layout of the external world. However, we need to be able to do more than just represent the world in spatial terms; we need to be able to act upon our representations. Therefore, one important

function of the dorsal stream is to participate in sensory-motor translation – transforming sensory representations into action patterns. These sensory-motor transformations allow a monkey to reach for an overhead branch at the correct location and then to form its hand into the correct shape for grasping the branch. Similarly, to search the sky for a bird whose song you have just heard, your brain must link up a spatial map of the world with eye-movement commands. To draw a sketch of a lovely vase of flowers requires translating the visual representation of the vase into movements of the hand to guide the pencil on the paper. For these reasons, some researchers prefer to think of the dorsal stream as a “how” pathway that contributes to planning action, rather than a “where” pathway that simply maps locations in space.

Constructional Abilities

We have examined the ability to perceive spatial relations but have not yet discussed the ability to motorically produce or manipulate items so that they have a particular spatial relationship. These latter abilities are often referred to as [constructional praxis](#). In everyday life, such abilities can be critical for tasks ranging from manipulating a key so that it fits correctly into a lock to picking up a bowl of pasta and scooping some onto your plate.

In the laboratory and the clinic, constructional skills are examined by tasks that are relatively simpler than the real-life instances just discussed. Such tasks can include copying a complicated nonsense drawing, building a block world, and manipulating and arranging colored cubes to match a particular pattern. The Rey-Osterrieth Complex Figure shown in [Figure 7.11A](#) is often used to assess spatial-constructional skills and perceptual skills. Most often, constructional abilities are disrupted by damage to the right hemisphere (e.g., Benton, [1967](#); Biesbroek et al., [2014](#)). The role of the right hemisphere in constructional tasks can be seen by looking at the copies of the Rey-Osterrieth Figure drawn by three individuals who had strokes that damaged the temporoparietal region of the right hemisphere (see [Figure 7.11B](#)).

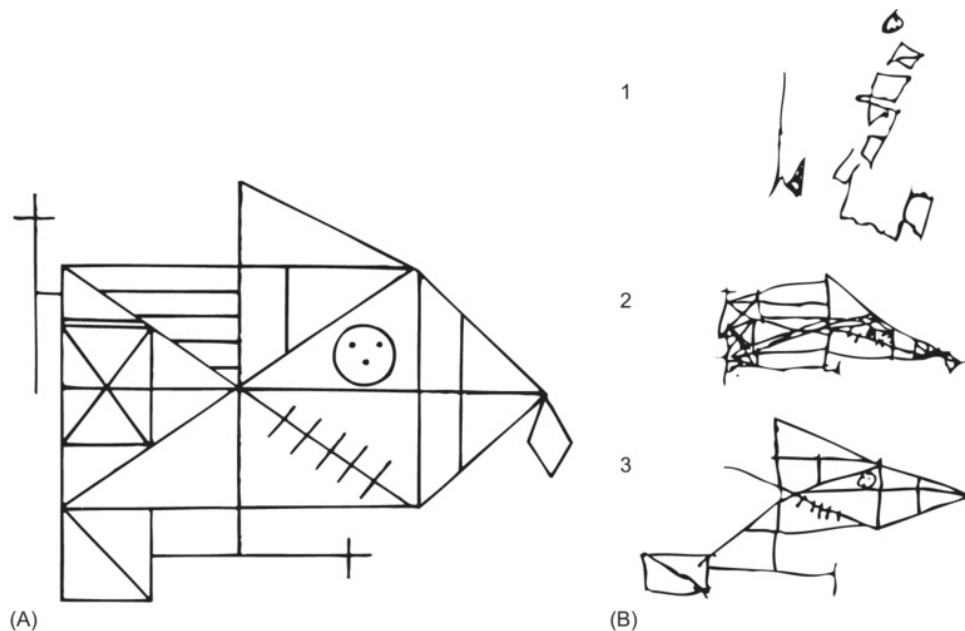


Figure 7.11 The testing of visuospatial drawing abilities.

(A) The Rey-Osterrieth Complex Figure (from Lezak, [1983](#)). (B) Examples of attempts to copy this figure by three individuals with damage to posterior sections of the right hemisphere.

(adapted from Benewitz et al., 1990)

Given the role of motor control in constructional tasks, you might wonder if such tasks really measure spatial representation skills at all, or whether they are simply measures of motor skill. Addressing this question, one study found that visuospatial abilities, such as judging line orientation, angle width, and geometric figures (assessed without a motor component involved), significantly predicted performance on visuomotor copying tasks, and this pattern held true for both neurologically normal people as well as patients with right-hemisphere damage (Trojano et al., [2004](#)). This study's results attest that spatial perception is a critical element of constructional praxis.

Neuroimaging evidence also demonstrates that both left and right parietal lobes are involved in drawing, one kind of constructional ability. For example, one study used fMRI to compare brain activity in a condition in which neurologically normal people either named pictures, or named the pictures and then drew them with the right hand (Makuuchi et al., [2003](#)). In the naming-plus-drawing condition compared to the naming-

alone condition, activation was observed bilaterally in the parietal lobes. Likewise, another imaging study asked participants to either trace over a sample image or to copy it onto a separate sheet (Ogawa and Inui, [2009](#)). Tracing and copying require execution of similar motor actions, whereas copying depends more on translating from a visual image to motor plans. Results from the study indicated that copying activated the intraparietal sulcus in both hemispheres to a greater degree than tracing.

One of the challenges in examining the neural basis of drawing, or other constructional tasks, as an example of space-action relationships is that so many different factors can contribute to performance on these tasks (Chechlacz et al., [2014](#)). It can be difficult to pin down exactly what mental operation is being studied in either a clinical study of constructional deficits or a neuroimaging study of constructional ability. For example, completing a drawing successfully depends upon spatial understanding and sensory-motor translation, but it also requires attention, planning, and fine motor control. Furthermore, various strategies may be enlisted when copying a drawing. For example, verbal strategies may be used to compensate for limitations in spatial understanding. Finally, drawing or copying may be disrupted in any number of ways, including poor overall spatial organization, poor inclusion of either local or global elements (look back on [Figure 6.16](#)), or neglect of portions of space. For all these reasons, although constructional difficulties are known to be a consequence of damage to the parietal lobe, the study of constructional abilities alone cannot definitively pin down neural mechanisms that are critical in translating sensory representations into motor actions.

Optic Ataxia

Another type of spatial deficit seen in patients with parietal lobe damage is [optic ataxia](#), which refers to a failure in visually guided reaching (Andersen et al., [2014](#)). Even when patients can verbally describe the location of targets, they misreach for them, indicating a problem in sensory-motor translation, not a problem in sensory

representation. [Figure 7.12](#) illustrates how a patient with optic ataxia may reach in the wrong place or orient the hand incorrectly when asked to fit her hand through a slot. The deficit is usually most pronounced in the peripheral rather than the central visual field. Interestingly, such patients often can use other cues, such as tactile or proprioceptive cues, to guide reaching. For example, a patient may easily complete a task in which she is asked to touch parts of her own body (e.g., touch your hand to your chin; touch your nose) while at the same time showing deficiency in reaching for an external object (Battaglia-Mayer and Caminiti, [2002](#)). This pattern indicates a specific deficit in using vision to guide reaching.

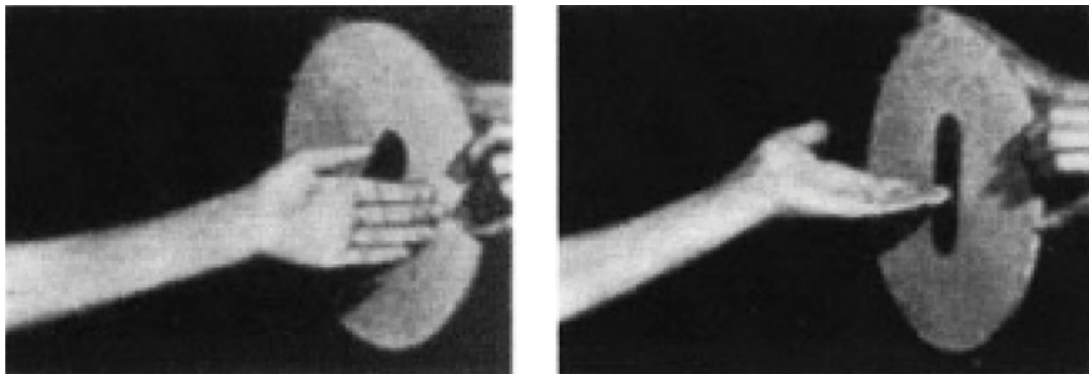


Figure 7.12 Example of deficits in visually guided reaching in a patient with optic ataxia.

The patient is unable to correctly reach her hand toward the location of the slot in the card or to orient the hand position correctly.

(from Battaglia-Mayer and Caminiti, [2002](#))

Patients with optic ataxia may also fail to take obstacles into account when reaching for an object. For example, imagine that you are reaching for your cup of tea, but the sugar bowl is in your path; you will direct your arm around or above the sugar bowl. In contrast, patients with optic ataxia do not do so (Schindler et al., [2004](#)). Other research has also found, somewhat counterintuitively, that the poor reaching performance of optic ataxics improves if there is a delay between the presentation of the target and the reaching movement (Milner et al., [2003](#)). This implies that the deficit is most profound

for real-time integration of vision and motion. Researchers have also proposed that optic ataxia may result from an inability to integrate cues involving eye-gaze direction and reaching direction (Jackson et al., [2009](#)).

Optic ataxia appears to be doubly dissociable from visual agnosia, which as you recall from [Chapter 6](#) is an inability to recognize objects based on visual information (Goodale, [2014](#)). In one case study, a patient with bilateral parietal damage could recognize line drawings of common objects but could not adjust the gap between her index finger and thumb to grasp these same objects (Jakobson et al., [1991](#)). In contrast, patients with damage to ventral extrastriate regions cannot recognize the size, shape, and orientation of visual objects, but can accurately guide both the hand and fingers to them (e.g., James et al., [2003](#)).

Evidence from TMS also supports the critical role that parietal regions play in controlling the direction of action in space. Researchers used tasks in which the participants had to make on-line adjustments in reaching and grasping movements as the location and size of a target changed in space. Imagine that you are trying to catch a Frisbee that a friend has thrown to you. To know how to position yourself for the catch, you have to continually update the visual information about the location of the Frisbee as it approaches you – an especially tricky task if it is a windy day or if your friend threw the Frisbee in a wobbly manner. TMS over the parietal regions impairs the ability of neurologically intact individuals to make these kinds of on-line adjustments (Della-Maggiore et al., [2004](#); Glover et al., [2005](#); Tunik et al., [2005](#)).

Studies of the clinical syndrome of optic ataxia in humans are prone to the same limitations as all studies of naturally occurring brain damage: lesions often cover a large amount of neural territory, and sometimes patients have other deficits as well that make it difficult to study one particular function, such as visually guided reaching, in isolation from other cognitive operations that may also be affected by the brain damage. In recent years, researchers have addressed these limitations by studying optic ataxia in monkeys with transient lesions selectively placed in specific parietal regions. Because reaching and grasping are natural behaviors for a monkey – unlike constructional tasks

such as copying the Rey-Osterreith Complex Figure! – the study of visually guided reaching is an aspect of sensory-motor control in which converging evidence from monkeys and humans with brain lesions can be synthesized.

Studies in monkeys have found that disrupting activity in a particular subregion of parietal cortex, known as the parietal reach region (PRR), produces symptoms much like those described in human optic ataxia. For example, pharmacological inactivation of the PRR in monkeys led to deficits in reaching for a target, even though eye movements to that same target were unaffected (see [Figure 7.13](#); Hwang et al., [2012](#)). The fact that eye movements to the target are not affected indicates that the monkey has a correct spatial representation of the target, but is unable to effectively use that information to guide reaching movements of the arm. Moreover, monkeys with lesions in this area were unable to use on-line information to adjust reaching movements – for example, when a target would suddenly change position – just as patients with optic ataxia have difficulty in using visual feedback to adjust reaching movements (Battaglia-Mayer et al., [2013](#)). Generally, these studies provide evidence for a particular subregion of parietal cortex that is crucial for supporting reach-to-target movements, an issue that we return to in greater detail below.

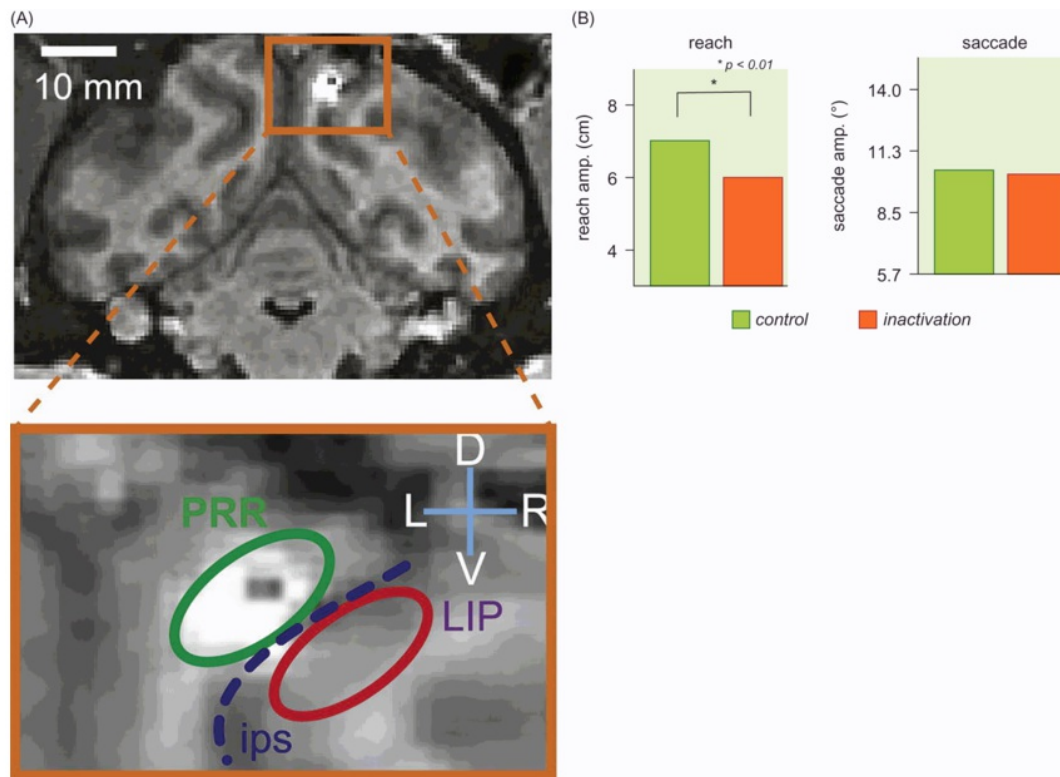


Figure 7.13 Inactivation of the parietal reach region in monkeys disrupts the ability to reach toward a target.

Panel A illustrates the region of parietal cortex that was transiently lesioned by injection of a pharmacological agent. PRR is the parietal reach region, tucked into the intraparietal sulcus (IPS). Panel B illustrates how, after inactivation of the PRR, reaching movements were impaired but eye movements (saccades) to the same target locations were normal. The LIP (lateral intraparietal cortex) appears to be more important in coding the spatial location of intended eye movements rather than reaches.

(from Andersen et al., [2014](#), who adapted it from Hwang et al., [2012](#))

Neural Mechanisms of Sensory-Motor Integration

While conditions such as optic ataxia illustrate the importance of parietal regions in supporting visually guided action, additional research is needed to address exactly how cells in the parietal region are able to connect sensory representations with action planning. Research using single-cell recording with monkeys has demonstrated that the cells in parietal cortex are well suited for sensory-motor integration (Andersen et al.,

[2014](#)). For example, a monkey is given a task in which he first fixates his eyes on a center spot on the screen, then observes a target stimulus flashed somewhere else on the screen. After a delay, he must reach his arm to that particular location. Cells in the parietal cortex are active when the target appears in the cell's receptive field, during the delay, and also during the movement (Batista et al., [1999](#)). The fact that the cell is active during the movement, even though the target is no longer present, suggests that the cell is not just coding sensory information about the location of an item.

Anti-saccade tasks have also been used to examine the role of parietal cells in sensory-motor transformations. In an anti-saccade task, a monkey sees a stimulus presented in a particular location, but must shift his eyes to a location away from the stimulus, rather than to the stimulus itself (see [Figure 7.14](#)). In this way, the anti-saccade task cleverly dissociates the location of sensory stimulation from the location of the intended movement. Cells in the lateral intraparietal cortex appear to code first for the location of the actual stimulus, but then, in less than 1 second, they change their firing to code instead for the location of the planned movement (the anti-saccade location) (Zhang and Barash, [2000](#)). Likewise, an EEG study in humans found that in an anti-saccade task, gamma-frequency oscillations (indexing coordinated neural activity) are first evident over the parietal lobe contralateral to the stimulus location, but then shift to the parietal lobe contralateral to the intended movement location (van Der Werf et al., [2008](#)). This converging evidence from monkey and human studies implies that parietal cells code for the spatial location of the intended movement even when it is different from the location of the sensory stimulus.

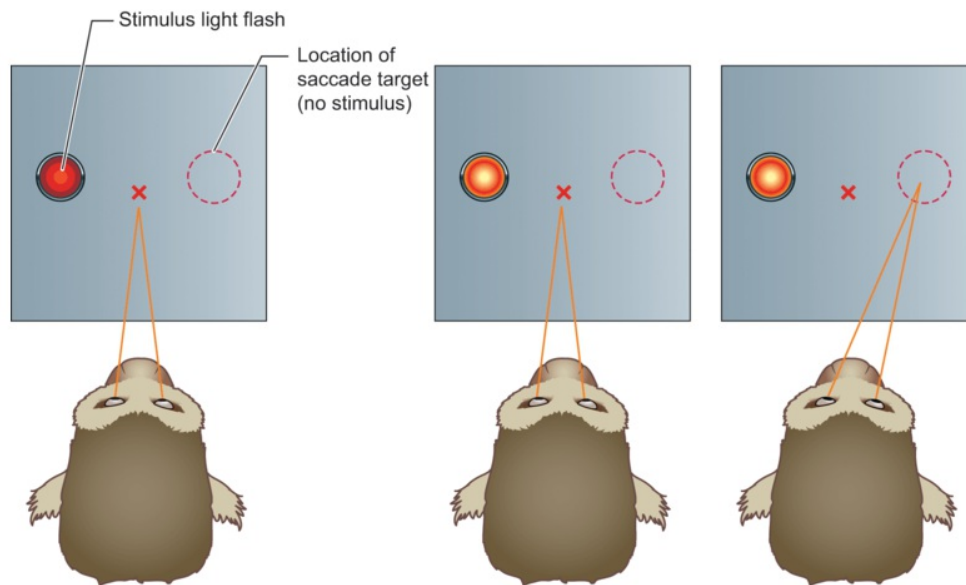


Figure 7.14 An anti-saccade task used to study sensory-motor translation.

In this task, a monkey sees a visual stimulus in one location, such as the left visual field, and must shift his gaze to the opposite location in order to see a treat/reward. Cells in parietal cortex code for the location of the intended movement, even though there is no visual stimulation in that location.

(Janzen and van Turenout, [2004](#))

Different subareas within the parietal cortex appear to contribute to the sensory-motor transformations necessary for different kinds of movements (Andersen et al., [2014](#)). As we discussed in the [previous section](#), evidence from studies with monkeys points to a reach-specific subregion of the parietal cortex, known as the PRR. Other evidence indicates that coding of space for intended eye movements takes place in a separate region, the lateral intraparietal region (LIP). For example, as illustrated in [Figure 7.15](#), one study found cells in the PRR that responded when monkeys were cued to reach an arm to a particular target, whereas other cells in the LIP responded when monkeys were cued to make an eye movement (saccade) to the same target location (Snyder et al., [1997](#)).

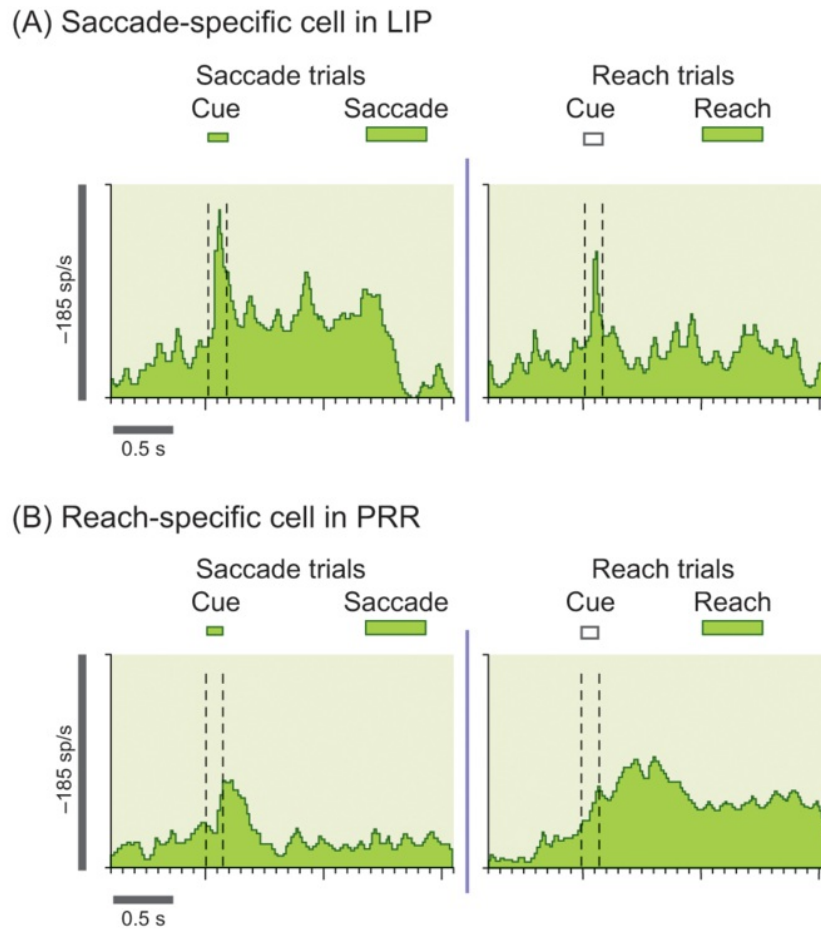


Figure 7.15 Parietal cells that code for either upcoming eye movements (saccades) or reach movements to targets.

Researchers recorded from individual cells in the parietal cortex of monkeys as they were cued to either move their eyes to a particular location (saccade trials) or reach to a particular location (reach trials). Cells in the lateral intraparietal cortex (LIP) showed increased activity after a saccade cue (panel A), whereas cells in the parietal reach region (PRR) showed increased activity after a reach cue (panel B).

Arm-reaching movements and eye movements must ultimately be connected in order to support hand-eye coordination – for example, allowing a baseball fielder to shift his eyes to track the changing position of an incoming fly ball while also reaching out to catch it with his mitt. However, the representations of visual space for the purpose of arm and eye movements appear to be at least somewhat separable before they are joined (Hwang et al., [2014](#)).

In addition to the distinct coding for saccade versus reaching movements, we can also consider the distinction between spatial coding for reaching versus grasping. The baseball fielder alluded to above must not only reach for the fly ball, but he must close his mitt around it at the right moment and with the right strength to grab it. Generally, we can think of reaching movements as being movements of the whole limb (the arm) to particular locations, whereas grasping movements refer to the shaping of the hand to fit the object. Reaching requires knowing an object's location, whereas grasping requires knowing its shape. Some patients with optic ataxia have difficulties with both visually guided reaching and grasping movements, suggesting the dorsal stream is important in supporting both functions. In addition, studies with monkeys indicate that separate populations of dorsal stream cells are critical for using visual cues to guide reaching versus grasping. Grasping in particular appears to be supported by an area known as V6, which is tucked inside the occipitoparietal sulcus and is in close connection with ventral stream regions that represent object shapes (Fattori et al., [2017](#)).

Human neuroimaging data also support the distinction between coding space for the movement of the hand and arm versus the eyes, although the precise mapping between parallel subregions in the human and monkey brain is still a matter of debate (Vesia and Crawford, [2012](#)). In human imaging studies, a task that involved planning eye movements activated a region on the lateral bank of the intraparietal sulcus, whereas a task that involved planning hand movements activated a more medial parietal region (Rushworth et al., [2001](#); see also Astafiev et al., [2003](#)). Additionally, an anterior region of the parietal cortex is activated during tasks that involve grasping or manipulating objects (Frey et al., [2005](#)). Therefore, there appears to be some segregation within parietal cortex such that different subregions assist in transforming spatial information into different kinds of actions.

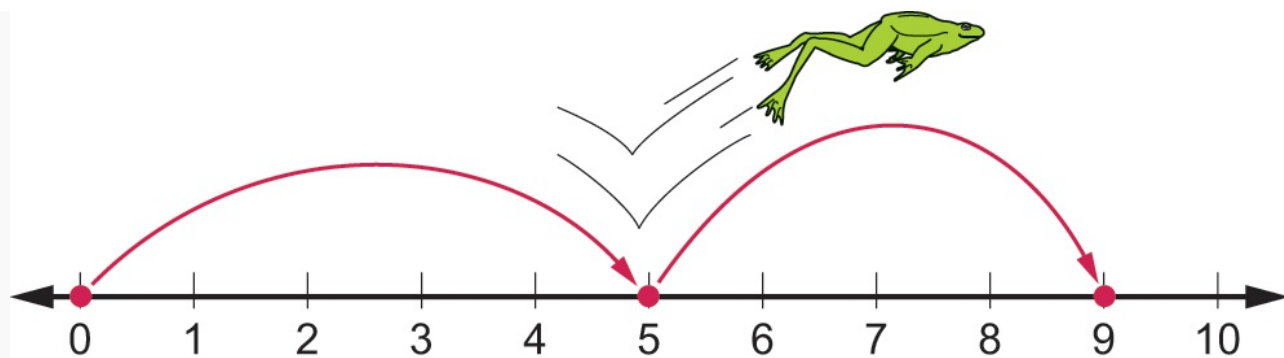
Together, then, studies of both monkeys and humans indicate that the spatial representations coded by the parietal cortex play an important role in guiding limb, hand, and eye movements to specific spatial locations. Next we investigate a different kind of movement: navigation through a large-scale environment.

Spatial Navigation

Our discussion so far has focused on spatial understanding within a relatively small scale, such as the spatial relations among a set of items in one's immediate view or within one's ability to reach and grasp. In everyday life, though, there is another crucial spatial skill, and that is the ability to navigate around an environment, an ability that is disrupted in the woman in the chapter's opening vignette. Navigation is an important skill in modern life, as we must find our way around city streets, neighborhoods, and university corridors. This skill was also important to our evolutionary ancestors, who had to navigate around a landscape that included thirst-quenching watering holes, reliable food sources, and areas of either shelter or danger.

In Focus: Are Numbers Spatial?

When you learned simple math as a kindergartner, your teacher probably used a number line as a teaching tool ([Box Figure 7.1](#)). On the number line, numbers are written from left to right, such that moving rightward along the line represents an increase in quantity. Simple addition and subtraction can be understood by the young child as movements back and forth along that number line. As you can see, the humble number line illustrates multiple ways in which numbers can be represented. There is a spatial element to the number line, as numbers are spatially ordered and greater numerosity disparities are represented as greater distances. At the same time, the number line also contains language-like symbolic representations, that is, the written numbers themselves ("1," "2," and so on). This deceptively simple representation gets straight to the heart of a debate about how the brain represents numbers, as well as more advanced mathematical processing: Are numerical and mathematical concepts represented spatially, linguistically, or in some other way?



Box Figure 7.1 A sample number line used by children when learning simple math.

Note that the number line has both spatial and symbolic elements.

First we must recognize the range of concepts that fall under the general rubric of “understanding numbers.” At the simplest level, even infants and many animals can make comparative quantity judgments, such as determining which of two piles has more apples in it. Such understanding of quantity does not require any symbolic or abstract representation of numbers. Furthermore, representations of approximate set size (two versus three, etc.) appear to be within the capability of both pre-literate children and other species. Monkeys can match a picture of three dots with a series of three tones, illustrating the cross-modal nature of number understanding. Yet, written number systems (“1,” “2,” etc.) are recent human cultural inventions found nowhere else in the animal kingdom. Furthermore, human mathematical capacity can extend far beyond addition and subtraction to encompass abstract mathematical concepts such as those you learned in algebra, geometry, and calculus. A challenge for cognitive neuroscientists is to understand how the brain supports this wide range of mathematical prowess.

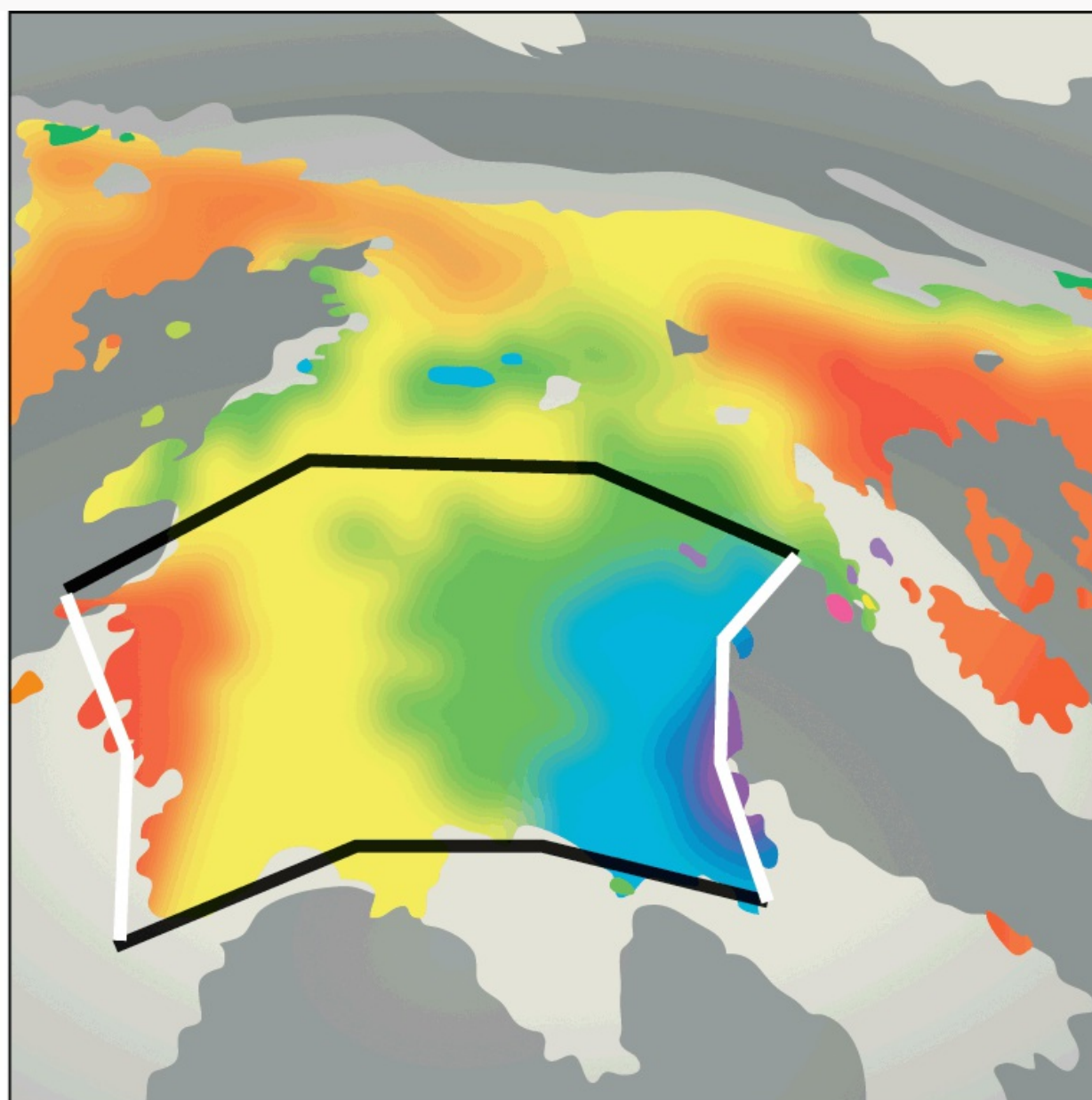
One clear conclusion from studies in both humans and monkeys is that basic number concepts appear to be represented by neurons within the parietal lobe, and particularly the intraparietal sulcus (IPS) (for review, see Nieder and Dehaene, [2009](#)). Neuroimaging studies have found that the IPS is activated by

changes in number representation, even when the form of the number representation changes from Arabic numerals to dot arrays or vice versa (Piazza et al., [2007](#)). For example, if the participant had seen repeated pictures of arrays of four dots, the IPS was activated when a different number was next presented in either dot array or Arabic number form, suggesting that the IPS had habituated (adapted) to the abstract concept of “four.” Illustrating the early developmental origins of the parietal representation of numerosity, one study presented 3-month-old infants with a series of pictures in which either the object shape or the number of objects could change (Izard et al., [2008](#)). Changes in number produced an electrophysiological response over the right parietal cortex, whereas changes in shape produced an electrophysiological response localized over ventral stream regions.

Likewise, single cells in monkey IPS appear to represent number, for example changing their level of activity when different numbers of dots need to be remembered during a delay (Nieder and Miller, [2004](#)). Although cells in prefrontal cortex also show sensitivity to numerosity as the monkey holds number information in mind during a delay, the IPS cells respond earlier than the prefrontal cells. This pattern suggests that the IPS first represents number information and then shares it with the prefrontal cortex during the working memory task. Thus, even in pre-literate research participants, the IPS appears to be important for representing information about numerosity.

How exactly are cells that represent number organized within the parietal cortex? Interestingly, monkey studies have found that numerosity-preferring cells are intermixed in the IPS with cells that code for other spatial features, such as line length (Tudusciuc and Nieder, [2007](#)). At the same time, human imaging studies have found a topographic representation of numerosity (at least for numbers 1 through 7), such that neighboring subregions of parietal cortex represent neighboring numerosities (see [Box Figure 7.2](#); Harvey et al., [2013](#)). In this sense, numerosity mapping in parietal cortex is similar to retinotopic

mapping in primary visual cortex or tonotopic mapping in auditory cortex, in that a particular property (in this case, number) is systematically mapped across a swath of cortex. The difference is that number is a more abstract, modality-general property that has to be computed, unlike retinal location or sound frequency, which are given more directly by the sensory input.



Preferred numerosity



1 2 3 4 5 6 7  1 cm

Box Figure 7.2 Topographic representation of numbers within a section of human parietal cortex.

Color represents the preference for responding to representations of the numerosity 1, 2, 3, and so on.

(from Harvey et al., [2013](#))

You might think that a parietal (and therefore probably spatial) representation is all well and good for simple number representation (e.g., comparing two approximate quantities or remembering the numerosity of a small set size), but what about other aspects of numerical cognition? In people who have learned to read, the written symbolic representation of a number (“1,” etc.) appears to activate a ventral stream region, analogous to the visual word form area that we discussed in [Chapter 6](#) (Hannagan et al., [2015](#)). But even beyond the visual representation of numbers, what about more complex operations that human mathematicians are capable of performing, such as algebra? It seems plausible that more complex mathematical understanding could be more language-like, given its reliance on both symbolic representation and syntactic rules.

Nevertheless, recent evidence suggests that even advanced mathematics depends less on language regions than one might suppose. Researchers asked professional mathematicians and control participants to evaluate the truth of different mathematical statements (e.g., “A finite left-invariant measure over a compact group is bi-invariant”) and nonmathematical statements (e.g., “In ancient Greece, a citizen who could not pay his debts was made a slave”) (Amalric and Dehaene, [2016](#)). For the professional mathematicians but not the control participants, evaluating the math statements led to increased activity (compared to nonmath statements) in a set of regions including left intraparietal cortex and left inferior temporal cortex, which are not traditionally considered to

be language areas. Interestingly, language areas were not differentially activated in the mathematicians evaluating the mathematical statements. Of course, this doesn't mean that language areas were completely inactive, but only that their activity did not increase especially in the mathematicians drawing upon advanced math knowledge, in the way that the parietal and inferior temporal regions did.

Generally, it seems that both simple numerosity judgments as well as advanced mathematical knowledge share a reliance upon common parietal lobe regions. This similarity occurs despite the fact that a simple understanding of numbers is found in pre-verbal infants and a wide range of species while advanced mathematical knowledge is obtained only by a small subset of humans. This raises interesting questions about the evolutionary basis for human numerical cognition. One hypothesis holds that advanced mathematical capabilities in humans – which, as a recent cultural invention, could not have been part of our evolutionary ancestry – piggyback upon evolutionarily older processes representing basic number knowledge. These older, core processes, such as evaluation of numerosity, are linked to spatial representation. Even the number line itself may have evolutionarily ancient origins, given evidence that newborn chicks appear to associate smaller numbers with the left side of space and larger numbers with the right (Rugani et al., [2015](#))!

According to this “core-knowledge” viewpoint, then, even as humans developed the capacity for symbolic representation and language (i.e., capacities that allowed for the visual symbolic depiction of numbers and complex knowledge about them), the system for numerical cognition was still anchored to an older, spatially based system. Indeed, evidence from cognitive studies in humans indicates that pre-linguistic number-sense skills strongly predict school math achievement (Halberda et al., [2008](#)). So the next time you see a child using

a number line or counting on her fingers, remember that she may be prepping her parietal lobes for learning calculus in the future!

Navigational Skills

People seem to invoke two basic strategies for spatial navigation, referred to as route-based versus cognitive map strategies. In route-based strategies, the person's understanding is represented as a sequence of steps, often specified in terms of particular landmarks. You are familiar with this kind of navigation from the typical driving directions you receive from a friend: go two blocks on Market Street, turn right at the gas station, turn left at the next stop sign, and my house is the third one on your right. This kind of spatial navigation does not require a map-like understanding of how the neighborhood is laid out. Rather it just involves being able to follow directions, by responding to a particular cue (stop sign) with the correct action (turn left). It is also egocentrically oriented, in the sense that the instruction "turn left" means "left" in relationship to you.

In contrast, a map-based strategy involves having an allocentric understanding of how all of the different parts of the landscape relate to one another. Such an understanding incorporates a mental map of the terrain to be traversed and one's position in that map at any given time. A person with map-like knowledge can still give and follow route-based directions, but this person is in better shape if she makes a wrong turn, because she understands enough about the spatial layout to create a new route to her goal.

Navigational skills can be assessed in a variety of ways. One task traditionally used to assess route-finding is the stylus maze task, in which the person must maneuver a stylus through an orderly array of identical bolt heads to reach a goal ([Figure 7.16](#)). Another task of route-finding ability requires a person to maneuver himself through a maze (rather than moving an object through a maze, as in the stylus maze task). In one such task, the locomotor maze, a series of nine dots is placed in a grid on the floor of a

large room (Semmes et al., [1955](#)). The person is given a map that designates a route, from start to finish, and he has to walk that route as quickly and accurately as possible. In addition to these traditional neuropsychological assessments, the development of virtual reality spatial environments has expanded the ability of researchers to manipulate aspects of an environment and observe effects on both a person's route-finding ability and the neural coding of that environment.

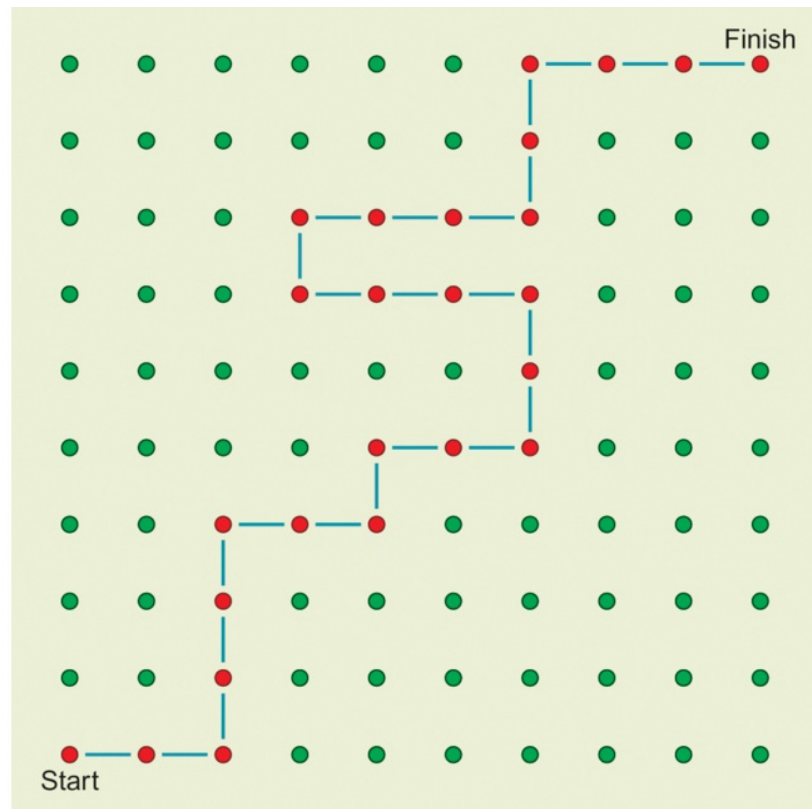


Figure 7.16 Example of a path that might have to be learned through the stylus maze.

The maze is an array of identical metal bolt heads, depicted here by circles. Although the path is shown in this diagram, it is not presented to the individual being tested. Rather, each time the person touches an incorrect bolt head, a loud click occurs. Thus, the individual must discover the correct direction of movement at each choice point and remember information about previously discovered portions of the maze.

Research with brain-damaged patients illustrates that spatial navigation can be disrupted in several different ways, in some cases affecting route-based strategies and

in other cases affecting cognitive map strategies (Aguirre, [2003](#)). The syndrome most closely tied to the dorsal stream pathways is [egocentric disorientation](#), which involves the inability to represent the location of objects in relationship to the self. This syndrome is associated with damage to the posterior parietal region, either bilaterally or unilaterally in the right hemisphere. Patients with this disorder have difficulties with navigation (both route-based and map-based) because they are unable to represent spatial relations. Performance is typically poor on other tasks of spatial understanding as well, such as spatial working memory tasks. Descriptions of navigational routes by these patients are severely impaired. Patients with this type of serious disorientation are often unwilling to venture out alone.

Navigational difficulties can also arise from problems elsewhere within the brain. For example, the syndrome called [landmark agnosia](#) is more like an object-recognition deficit than a true spatial deficit, although it does disrupt wayfinding ability. In this syndrome, patients lose the ability to recognize certain landmarks that are usually used for navigation, and therefore route-based navigation becomes difficult. For example, a patient may fail to recognize his house or his bedroom. Such patients often perform well on other spatial tasks, and their deficits typically occur following damage to ventral stream areas rather than dorsal areas. The deficits tend to involve damage to the medial surface of the occipital lobe, including a region known as the lingual gyrus as well as the parahippocampal gyrus (Aguirre, [2003](#)).

Additional navigational deficits implicate other brain regions. For example, damage to the parahippocampal gyrus can also lead to [anterograde disorientation](#), in which a patient is unable to construct new representations of environments, although she is still able to navigate successfully around previously known or previously learned environments (Epstein et al., [2001](#)). Furthermore, damage to the retrosplenial cortex can result in a syndrome labeled [heading disorientation](#), in which the patient is able to recognize landmarks and understand relations between locations in space, but has trouble understanding his own orientation (or heading) with either a familiar or unfamiliar environment (e.g., Hashimoto et al., [2010](#)).

Generally speaking, the fact that spatial navigation can be disrupted in multiple ways tells us that there are multiple component processes contributing to successful navigation. Furthermore, this evidence implies that there are likely to be different neural systems that play distinct roles in supporting the ability to navigate through an environment. In the [next section](#), we learn more about current models of how distinct yet interconnected neural regions contribute to wayfinding.

Neural Coding for Spatial Environments

Current models of spatial navigation propose that three main brain regions, heavily interconnected with one another, play distinct roles in navigation. [Figure 7.17](#) illustrates where these regions are located anatomically and depicts the aspect of spatial navigation that each is proposed to support. In brief, the parahippocampal place area (PPA) is thought to code for landmarks that are relevant to navigation; the retrosplenial complex (RSC) is thought to determine the person's location within a familiar spatial environment; and the medial temporal lobe (MTL; including hippocampus and related structures) contains a map-like allocentric representation of familiar environments (for review, see Epstein and Vass, [2014](#)). Below, we consider the role of each of these regions separately.

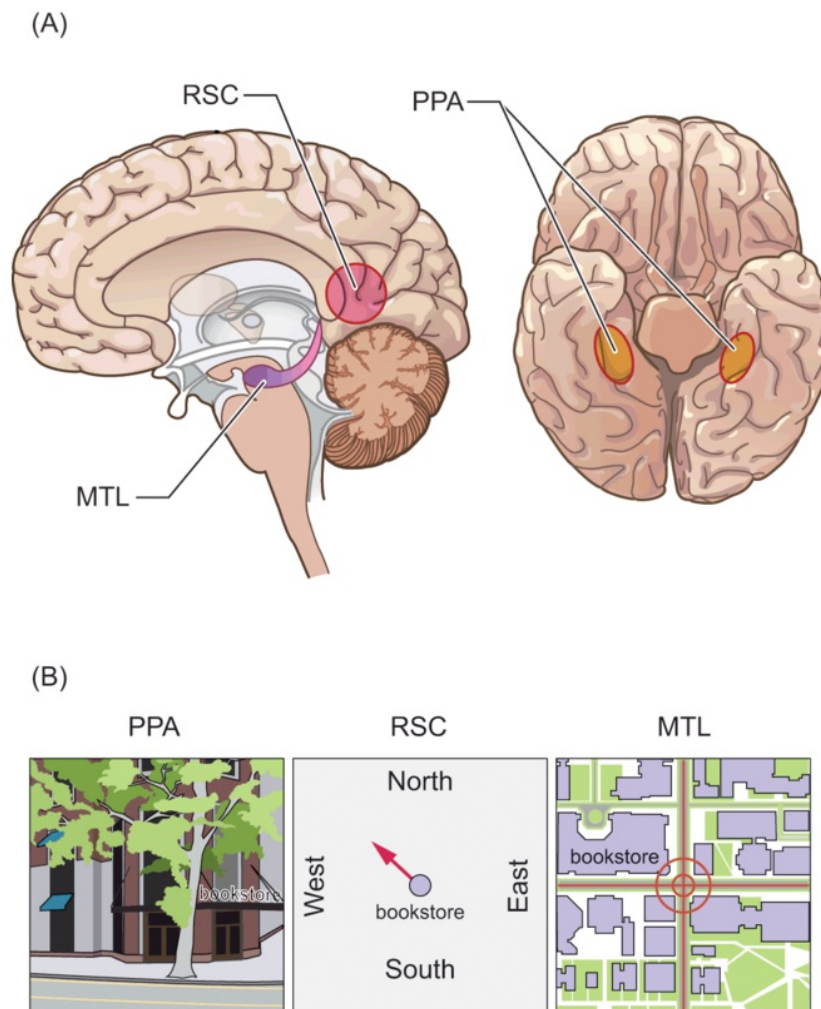


Figure 7.17 Depiction of three main regions relevant to spatial navigation and their proposed roles.

Panel A depicts the parahippocampal place area (PPA), the retrosplenial cortex (RSC), and the medial temporal lobe (MTL). Panel B depicts the navigational function each of these regions is thought to support. The PPA encodes landmarks, the RSC uses landmark information to determine where the person is positioned within an environment, and the MTL contains map-like representations of external environments.

Parahippocampal Place Area

We first encountered the PPA in [Chapter 6](#), during our discussion of ventral stream areas that are specialized for recognition of particular categories of visual objects. The PPA is a subregion of the parahippocampal cortex that is particularly involved in recognizing

landmarks that are used in navigation. In the natural world, landmarks could include a particular mountain crest, streambed, or grove of trees, and in the artificial world where most of us now live, landmarks could include buildings, street corners, or statues. Generally, landmarks have fixed locations (it wouldn't make sense to use a bicycle as a landmark, for example) such that they can be used as reference points in wayfinding.

In one study of landmark use (Janzen and van Turenhout, [2004](#)), participants learned to navigate around a novel environment presented on a computer screen. Some objects were encountered at “decision points” in the route through the novel environment. (These objects are analogous to the stop sign where your friend's directions tell you to turn left.) Objects associated with such decision points were more likely to activate parahippocampal regions compared to objects that were encountered but not relevant to a choice point in the route (see [Figure 7.18](#)). These findings support the idea that the parahippocampal region is especially involved in coding for landmarks that are important for navigation.

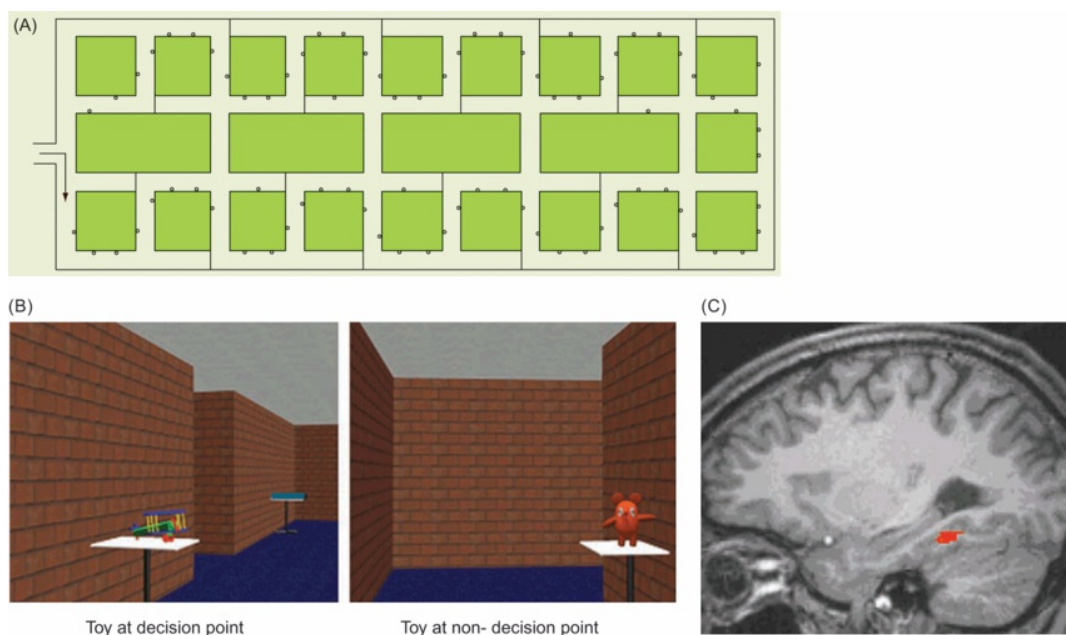


Figure 7.18 Brain areas activated by landmarks in navigation.

In this study (Janzen and van Turenout, [2004](#)), participants navigated through a virtual maze, shown in panel A. Cartoon toys (see panel B) were placed in certain locations in the maze. Some toys were placed at decision points in the maze, where the participant had to decide which direction to go, and other toys were placed at nondecision points. Brain imaging data showed that the parahippocampal gyrus (see panel C) was more activated by pictures of toys that marked decision points than by toys that were present in the maze but did not mark a decision point.

Interestingly, the PPA appears to code for familiar landmarks in an abstract manner that is independent of the visual representation of the landmark. The best example of this characteristic comes from a study that found that the PPA responded similarly to pictures of both the interiors and exteriors of familiar buildings (Marchette et al., [2015](#)). Participants were shown pictures of both inside and outside views of familiar places on their university campus, such as the university bookstore and the gym. Even though the inside of the bookstore looks very different than the outside of the bookstore, they both represent the same landmark (and likewise, the inside and outside views of the gym both represent the same landmark, albeit a different one than the bookstore). Researchers found that the pattern of activity evoked in the PPA by the inside view of a familiar

building (such as the bookstore) was closely related to the pattern evoked by the outside view of that same building, and yet distinct from the pattern evoked by the inside or outside view of a different building (such as the gym). These findings reinforce the role of the PPA in representing particular places.

So is the PPA part of the ventral stream or dorsal stream? The answer may be “both,” in a sense. Like other specialized ventral stream areas, the PPA uses visual information to recognize specific objects (in this case, landmarks). Likewise, damage to the PPA may result in a specific kind of visual recognition deficit, landmark agnosia. Nevertheless, the PPA is highly interconnected with regions that we would classify as part of the dorsal stream, such as posterior parietal cortex, and it participates in a clearly spatial function, wayfinding. In a sense, the question about whether the PPA is a ventral or dorsal stream region points to the limitations of dichotomous models that segregate brain regions into independent categories. Some functions, such as spatial navigation, may draw upon component processes that can’t be easily classified. In a later section, we return to the limitations of the dorsal–ventral stream dichotomy.

Retrosplenial Cortex

The RSC is an area on the medial surface of the parietal cortex, just posterior to (behind) the corpus callosum (look back on [Figure 7.17](#)). The posterior portion of the corpus callosum is called the splenium, so the name “retrosplenial” very descriptively locates this region (behind the splenium). The RSC is closely anatomically connected with other regions relevant to spatial navigation, including other parts of the posterior parietal cortex and medial temporal regions.

Studies in other species have found that spatial navigation is disrupted when the RSC is damaged experimentally (e.g., Haijima and Ichitani, [2008](#); Pothuizen et al., [2008](#)). In addition, recordings from RSC cells in rats navigating through environments have shown that these neurons can code for space in multiple reference frames. For example, analysis of the firing patterns of RSC neurons found that ensembles of these

neurons can code for the rat's right or left turning behavior (egocentric coding) as well as coding for the rat's position within the larger environment (allocentric coding) (Alexander and Nitz, [2015](#)). Such results have led to the proposal that the RSC contributes, in ways not yet fully understood, to integration between different reference frames (e.g., egocentric and allocentric).

Imaging studies in humans have also helped to establish the unique contribution of the RSC. For example, one study found that the RSC was more activated when people viewed a scene and had to recall its location (east or west of a landmark road) or orientation (facing east or west), compared to when they simply had to say whether the scene was familiar; in contrast, the parahippocampal cortex was activated by viewing scenes regardless of the type of judgment made about them (Epstein et al., [2007](#)). These results imply that the RSC plays a particularly important role in memory retrieval regarding a location in the environment.

Furthermore, the RSC is able to code for location in a familiar environment regardless of the facing direction within that environment. For example, one study asked participants to view pictures of familiar intersections and to decide whether the picture was taken facing north, south, east, or west (a decision that could only be made by someone familiar with that environment!). Pictures of the same intersection shown with different facing directions (e.g., corner of 30th and Market Street shown facing north, south, east, or west, with no overlapping visual elements) evoked similar patterns of activity in the RSC, whereas pictures of different intersections evoked different patterns of activity (Vass and Epstein, [2013](#)). In other words, the RSC appeared to have a unique code for specific spatial locations (e.g., familiar intersections) that is activated no matter what orientation the viewer occupies within that location. At the same time, other evidence indicates that the RSC is also able to preserve information about facing direction (heading) as well; in other words, not just "I'm at 30th and Market" but "I'm at 30th and Market facing north" (Vass and Epstein, [2016](#)). These data support the view that the RSC is concerned with representing one's location in a large-scale environment.

Medial Temporal Lobe

In addition to the PPA and RSC, medial temporal lobe (MTL) regions such as the hippocampus also play a role in spatial navigation (look back on [Figure 7.17](#)). Much of the early evidence for the role of MTL regions came from research in nonhuman species. For example, damage to the hippocampal complex in rodents produces severe problems in environmental navigation (Morris, [1981](#); Sutherland et al., [1983](#)). Classic studies in rats also demonstrated the existence of so-called “place cells” within the hippocampus, in work that earned the 2014 Nobel Prize in Physiology and Medicine for researchers John O’Keefe, May-Britt Moser, and Edvard Moser (O’Keefe and Dostrovsky, [1971](#); see Hartley et al., [2014](#), for review).

A place cell is active when the animal is located in a particular place in its local environment, no matter which way the animal is facing or which route he took to get there. [Figure 7.19A](#) illustrates the response of a typical place cell as a rat moves around an environment. Because different hippocampal place cells respond preferentially to different locations, a population of place cells has the ability to code for the animal’s location anywhere within an environment. Coding of specific places by these cells is reliable enough that by examining the pattern of activity across a population of place cells, researchers can easily determine where the animal is located.

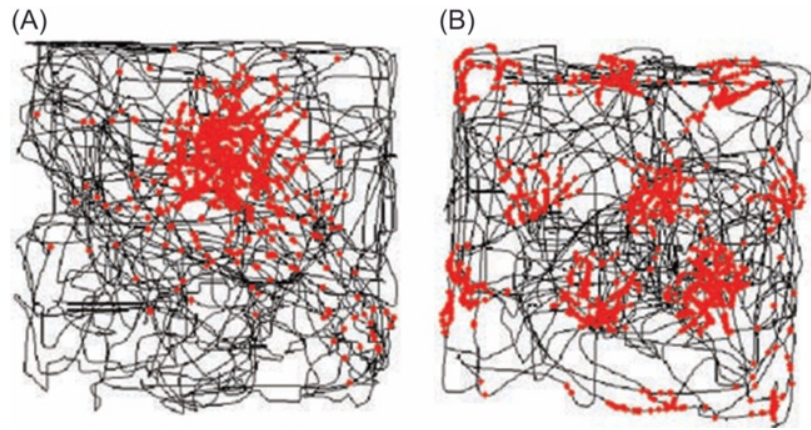


Figure 7.19 Responses of location-specific cells in a rat.

Dark lines show the rat's path as it runs around an enclosure. Superimposed red lines show locations that cause a particular cell to fire. Panel A shows the response of a typical hippocampal place cell, which fires when the rat is in a specific place within the environment. Panel B shows the response of a typical grid cell in the medial entorhinal cortex. The grid cell responds to several spatial locations that are organized in a grid-like pattern.

(from Moser et al., [2008](#))

Other cell types within the MTL also have properties that reflect coding for position within a spatial environment (Hartley et al., [2014](#)). For example, the entorhinal cortex (which projects directly to the hippocampus) contains “grid cells” that respond to multiple spatial locations that are organized in a grid-like fashion (see [Figure 7.19B](#)). The hippocampal complex also includes head-direction cells, which fire when the animal is facing in a particular direction, and border cells, which fire when the animal is near a border within its environment.

Recent studies support the idea that the human brain, too, contains cells in the MTL that code for spatial location in an environment. For example, one study recorded from individual cells in the MTL – including hippocampus and parahippocampal cortex – in epileptic patients about to undergo surgery who were exploring a novel “town” through a computer-based virtual reality system (Ekstrom et al., [2003](#)). Hippocampal cells tended to respond best to specific spatial locations (as had been previously

demonstrated with rodents), whereas parahippocampal cells tended to respond best to views of certain landmarks. Another study using similar methodology found evidence for grid cells in the human entorhinal cortex (Jacobs et al., [2013](#)).

Neuroimaging studies with humans also imply that the hippocampus is important for navigational abilities in people, just as in rodents. One famous study examined hippocampal activity among taxi drivers in London (Maguire et al., [1997](#)). London taxi drivers are experts at knowing the topography of the city: they must train for approximately three years and pass a stringent test to obtain a license. The taxi drivers exhibited significantly more activation of the right hippocampus when asked to remember specific routes, compared to when they just had to remember landmarks. The size of the right posterior hippocampus predicts cognitive map knowledge in both London taxi drivers (Woollett and Maguire, [2011](#)) and college students learning their way around a new campus (Schinazi et al., [2013](#)).

The hippocampal contribution to navigation may be unique (in comparison to other navigation-related brain regions) in its precise metric representation of distances between locations in an environment. Supporting this idea, one study found that when college students viewed pictures of campus landmarks that differed in distances from one another, the response of the left hippocampus was correlated with the metric distance between landmarks shown on successive trials (Morgan et al., [2011](#)). In contrast, neither the PPA nor the RSC showed this distance sensitivity.

In sum, wayfinding in a complex, large-scale environment depends on several component skills that appear to be carried out by several different brain regions working in concert. Your ability to find your way back to your apartment after a night on the town (or the ability of the taxi driver whom you hire!) likely depends on recognition of landmarks (“there’s the statue in the park”), orienting yourself using those landmarks (“I must be at the park, facing east”), and map-like knowledge (“this is going to be a long walk, or an expensive taxi ride, because I know I am far from home”). Working together, a well-functioning PPA, RSC, and MTL will get you there.

Challenges to the Dorsal-Ventral Stream Dichotomy

Throughout most of this chapter, we have emphasized the importance of dorsal stream regions in various aspects of spatial perception, in contrast to the ventral stream regions important in object recognition, which we discussed in [Chapter 6](#). The distinction between these two processing streams has provided a powerful way of organizing our understanding of the various complex visual tasks that the brain must perform. However, we must also be aware of the limitations of a simple model that divides processing so starkly between the dorsal and ventral streams (de Haan and Cowey, [2011](#); Husain and Nachev, [2007](#)).

First, it is important to recognize that spatial functions are not completely segregated to the parietal region of the brain. Although the parietal lobes are extremely important in spatial cognition, they are not the only brain regions involved. As we learned in this chapter, other brain regions also play a role in certain aspects of spatial processing. Among these are the hippocampus and parahippocampal regions, important in spatial memory and navigation. Likewise, the parietal lobe is not solely dedicated to spatial functions. It also plays an important role in attention, as we will learn in [Chapter 10](#).

Remember also that some processes are important in both spatial understanding and object recognition. Therefore, some types of information are represented in both dorsal and ventral streams, but for different purposes. For example, the shape of an object is represented by cells in the lateral intraparietal area in a way that preserves information about the object's size and position; this representation is useful for guiding grasping movements (Janssen et al., [2008](#)). In contrast, cells in the ventral stream represent an object's shape in a size- and position-invariant manner, which is useful for recognizing the object's identity.

Depth and movement cues are also important for both ventral and dorsal stream processes. Depth perception allows a three-dimensional understanding of an object, which is important in object recognition. Motion perception can also be useful in

recognizing an object. For example, you may be able to tell whether a dark form in the distance is a dog or a bear, depending on whether its motion is bounding or lumbering. Therefore, it should not be surprising that motion processing area MT feeds into the ventral stream as well as being part of the dorsal stream. Spatial navigation provides another example: one way we work our way around space is by recognizing certain landmarks such as buildings and signs, a ventral stream process. These examples remind us that the functions carried out by the dorsal and ventral streams are related to one another, if still separable. In fact, much recent research is focused on elucidating how the dorsal and ventral processing streams interact (e.g., Sim et al., [2015](#); van Polanen and Davare, [2015](#)).

Summary

The Dorsal Visual System for Spatial Cognition

- The perception of spatial relations depends heavily on the parietal lobe, which is part of the dorsal, or “where,” visual system.
- The dorsal stream incorporates three different substreams, including a path connecting to prefrontal cortex for purposes of spatial working memory, a path connecting to premotor cortex supporting visually guided actions, and a path connecting to medial temporal lobe supporting spatial navigation.
- Single-cell recordings indicate that cells in the parietal region are sensitive to a combination of eye and head position, and are sensitive to motion in the range of speeds at which animals locomote – all of which make them well suited for processing spatial relations and constructing a map of external space.

Coding for the Three Dimensions of Space

- Damage to the parietal cortex can result in the inability to distinguish the left and right orientations of objects.

- Depth can be coded by binocular disparity (comparing inputs from the two eyes) or by motion parallax (comparing how objects move across the retina as the animal moves through space). Cells in the dorsal stream are sensitive to both binocular disparity and motion parallax, indicating an integrated coding for depth.

Spatial Frames of Reference

- Spatial positions can be coded with respect to some aspect of the self, known as an egocentric reference frame; or with respect to external references, known as an allocentric reference frame.
- Evidence from monkeys suggests that cells within the parietal cortex can code for spatial location in multiple reference frames, including head-centered, eye-centered, and object-centered.
- Evidence from brain-damaged patients indicates that different kinds of egocentric and allocentric coding can be independently disrupted, indicating that they rely on separable brain processes.
- The left hemisphere is specialized for determining categorical spatial relations, in which the relationship of two points is described according to categories of locations (above versus below, to the left versus to the right), whereas the right hemisphere is specialized for computing coordinate (metric) spatial relationships that specify the distance between two points.

Motion Perception

- Studies of brain-damaged patients and neuroimaging studies indicate that a specific region, area MT (V5), at the juncture of the parietal and temporal lobes, is critically important for perceiving motion. A neighboring region, MST, is also involved in coding for more complex motion, such as optic flow.

- To accurately understand whether external objects are moving or stationary, the person must take into account the body's own motion. Parietal lobe regions receive input from the vestibular system and from areas controlling and sensing eye movements, so that the movement of external objects can be calculated in reference to the self.

Space and Action

- Difficulties in spatial construction, such as drawing and building with blocks, can be seen in patients with damage to the dorsal stream.
- Optic ataxia is a disorder of visually guided reaching that illustrates the importance of the parietal lobe in integrating perception and action.
- Cells in the parietal region are essential for translating a perceptual understanding of space into actions toward specific spatial locations. Different subregions of the parietal cortex are involved in coding for intended eye movements and arm movements toward targets.

Space and Number

- Representations of numerosity (how many) are found in the dorsal stream, particularly in the intraparietal sulcus, in both humans and monkeys.
- Current models propose that advanced mathematical capabilities in humans are built upon an evolutionarily older “number sense” that is localized in parietal cortex.

Spatial Navigation

- Navigating through large-scale space can rely upon either route-based or map-based representations.

- Three key regions involved in spatial navigation are the parahippocampal place area, which responds to landmarks; the retrosplenial cortex, which represents location; and the hippocampus and related medial temporal regions that contain map-like knowledge of a familiar environment.

Chapter 8

Language



[Brain Systems for Auditory Language](#)

[Classic Neurological Conceptions](#)

[Psycholinguistic Perspectives](#)

[Phonology](#)

[Syntax](#)

[Semantics](#)

[Evidence From Double Dissociations](#)

[Language Processing From a Network Perspective](#)

[Reduced Evidence for Language-Dedicated Regions](#)

[Overlap of Syntactic, Semantic, and Phonological Processing](#)

[Interacting Brain Regions Enable Language Processing](#)

[Visual “Spoken” Language](#)

[Basic Structure of American Sign Language \(ASL\)](#)

[Neural Organization of ASL](#)

[In Focus: Brain Organization in Bilinguals](#)

[Neurological Bases for Visual Language Processing](#)

[Evidence From Studies of Patients With Brain Damage](#)

[Alexia Versus Agraphia](#)

[Reading](#)

[Writing](#)

| |
|--|
| Converging Evidence from Other Research Methods |
| Processing of Non-Indo-European Languages and Other Symbolic Systems |
| Kana and Kanji |
| Music |
| Right-Hemisphere Contributions to Language Processing |
| Prosody |
| Semantics |
| Narrative, Inference, and Metaphor |
| Summary |

Dr. Sheila Chorpenning, a neurologist, had just joined the staff of a hospital for US Army veterans. In the large patient recreation room, she noticed two men sitting on a sofa, one middle-aged and one younger. The middle-aged man, Bill Rieger, had been a rising star in high school – academically talented and a top athlete. But then his mother died unexpectedly. Confused by her death, he turned down a scholarship to college and joined the army. During a combat mission, he was hit by shrapnel that damaged his left frontal lobe as well as parts of his parietal lobe. Dr. Chorpenning introduced herself and asked Bill to tell her about his history. He replied:

My un mother died ... uh ... me ... uh fi'tenn. Uh, oh, I guess six month ... my mother pass away. An'uh ... an'en ... un ... ah ... seventeen ... seventeen ... go ... uh High School. An uh ... Christmas ... well, uh, I uh ... Pitt'burgh.

(Goodglass, [1976](#), p. 239)

He told the story with much effort, and the words seemed to explode as they came out of his mouth. His intonation was uneven, which made his speech difficult to follow initially, but with time Dr. Chorpenning found him easier to understand.

The younger man, who was in his late twenties, was named Jim Hurdle. He had had a carotid artery aneurysm (the ballooning, then breaking of the carotid artery), which had caused brain damage. As Dr. Chorpenning began to converse with him, he attempted to explain that he didn't live at the hospital but had just been brought there by his father to have some dental work performed:

Ah ... Monday ... ah, Dad and Jim Hurdle [referring to himself by his full name] and Dad ... hospital. Two ... ah, doctors ..., and ah ... thirty minutes ... and yes ... ah ... hospital. And, er Wednesday ... nine o'clock. And er Thursday, ten o'clock ... doctors. Two doctors ... and ah ... teeth. Yeah, ... fine.

(Goodglass, [1976](#), p. 238)

Like the first man, Jim spoke in a slow, halting cadence, and his words were produced in a harsh and guttural manner.

Despite their difficulties in speaking, both men seemed to understand most of what Dr. Chorpenning said to them. When she mentioned that the weather was spring-like, Bill pointed to the open window through which a warm breeze was blowing. When she discussed what a relief the present weather was compared with the cold, hard winter that they had been experiencing, Jim pulled his sweater tightly around himself and imitated a shiver. Before she left, she thanked both men for chatting with her, realizing how frustrated they were with their inability to communicate.

Language is the mental faculty that many people consider most uniquely human and that most distinctly separates us from the other species that inhabit the earth. Language is also a function that has long been studied by scientists. Symptoms like those experienced by Bill Rieger and Jim Hurdle first led Paul Broca in the late 1800s to realize that the hemispheres have different functions, an event that heralded the advent of

modern-day neuropsychology and cognitive neuroscience. Broca noticed that a lesion to a specific region of the left hemisphere causes a loss of fluent speech even though the person's speech comprehension is relatively spared. This syndrome, known as [Broca's aphasia](#), has provided a window to understanding the neurological organization for language.

Aphasia is the loss of a language processing ability after brain damage (for review see Tippett et al., [2014](#)). In this chapter, we discuss a variety of aphasias, gleaned from each some lessons about the neurological organization for language. We consider the neural underpinnings of spoken and written language and examine the degree to which their neural substrates are both similar and distinct. Although most of our discussion focuses on the neural organization for Indo-European languages, such as English, we also consider the neural underpinnings of other languages, including languages from Asia and languages created by people who are deaf. If some aspects of the neurological organization for language are universal, they should reveal themselves despite the different grammatical structures found across languages (e.g., Indo-European versus Asian languages) and despite differences in the modality in which the information is conveyed (e.g., sound in English versus hand movement in American Sign Language). We end the chapter by examining how the right hemisphere, which was initially thought to be relatively uninvolved in language, contributes to language processing.

Brain Systems for Auditory Language

We know from individuals with aphasia and from patients with the split-brain syndrome (see [Chapter 2](#)) that the left hemisphere plays a leading role in speech production. This fact is supported by two methods used during surgery for epilepsy to isolate brain regions involved in language processing. One of these, the Wada technique, was discussed in [Chapter 2](#). As a reminder, this procedure involves the injection of sodium amobarbital, a barbiturate, into one of the two carotid arteries, causing only one of the hemispheres to become anesthetized. After the drug takes effect, the test administrator

asks the patient to name a series of items, which the administrator has confirmed the patient could name prior to injection. If the anesthetized hemisphere is responsible for speech output, the person will be unable to name the items. Typically the procedure is repeated the next day with the opposite hemisphere (Grote et al., [1999](#)). This second injection is necessary even if speech was disrupted by the first anesthetization, because in a relatively small percentage of cases speech output is controlled by both hemispheres.

[Table 8.1](#) presents the percentages of left- and right-handed people who have left-hemisphere, right-hemisphere, and bihemispheric control of speech output as determined by the Wada test in a classic study (Rasmussen and Milner, [1977](#)). These percentages accord well with more recent data on lateralization for language inferred from speech arrest after the administration of TMS in neurologically intact individuals (Khedr et al., [2002](#)). Due to this concordance between the Wada test and less invasive measures, some scientists have suggested that the Wada technique could be replaced by fMRI (Baxendale, [2009](#)). However, in a notable (although small) percentage of cases, fMRI does not provide converging information with that obtained with the Wada technique (Bauer et al., [2014](#); Połczyńska et al., [2015](#)) so the Wada technique remains in use today in clinical practice.

Table 8.1 Control of Speech Output in a Sample of Left- and Right-Handed Patients as Determined by the Wada Technique

| HANDEDNESS | # OF CASES | SPEECH REPRESENTATION (%) | | |
|------------|------------|---------------------------|-----------|-------|
| | | LEFT | BILATERAL | RIGHT |
| Right | 140 | 96 | 0 | 4 |
| Left | 122 | 70 | 15 | 15 |

As you can see from [Table 8.1](#), speech output is rarely controlled by the right hemisphere in right-handed people, and in no case is speech output controlled by both hemispheres in right-handers. This information is consistent with the clinical observation that [crossed aphasia](#) – that is, aphasia resulting from a right-hemisphere lesion in a right-hander – occurs with a frequency of 1% or less (Benson and Geschwind, [1972](#); Hoffman and Chen, [2013](#)).

Language organization is more varied among left-handers than right-handers. Although left-handers, like right-handers, are most likely to have speech output controlled by the left hemisphere, in a significant proportion of left-handers the right hemisphere is specialized for speech output. Furthermore, in still other left-handed people, each hemisphere is capable of producing speech, a pattern rarely if ever observed in right-handers.

Another means of investigating the localization of language is to stimulate the brain electrically before or during surgery for the removal of epileptic tissue (see Hamberger, [2007](#), for a review). This procedure is referred to as cortical stimulation mapping. We previously discussed using stimulation to determine the location and extent of the motor and somatosensory regions (see [Chapter 2](#)); a similar stimulation method is used to map areas crucial for language. The stimulation method reveals that language is lateralized to the left hemisphere in nearly all right-handers, a finding consistent with the results of lesion studies and the Wada test (e.g., Wylie et al., [1990](#)). While this technique tells us that the left hemisphere plays a primary role in language output, we now examine in more detail exactly how it is organized for different aspects of language function.

At the beginning of this book, we discussed how the relationship between the brain and mental function can be examined from either of two vantage points: one emphasizing the neurological organization of the brain, and one emphasizing the psychological processes performed by the brain. These two vantage points are well illustrated by the differing perspectives on language breakdown after brain trauma.

The early classic advances in this field, made in the mid- to late 1800s, came squarely from a neurological, or medical, perspective in which physicians characterized

the patterns of language impairment that accompany specific brain lesions. Because damage to particular regions of the cortex can each produce distinct language problems, the early aphasiologists (i.e., people who study aphasia) proposed that each region of the cortex had a predominant role in language processing: one area was viewed as playing a predominant role in recognizing sound images of words, while another was supposed to be predominant for producing speech. According to these models, the brain processes language much as a factory manufactures products along a conveyor belt. Input is received at one region, then is packaged and sent to another region for output. These models have a “knee bone is connected to the thigh bone” feel to them.

Since the 1960s, psycholinguists have examined the neurological bases for language from a different perspective. In attempting to understand the effects of brain damage on language processing, these researchers have emphasized the organization of language rather than the organization of the brain. This approach has led them to ask very different questions about aphasia. For example, they have used aphasia to help test theories about the fundamental components of language.

In this chapter, we examine language processing from both perspectives, the neurological and the psychological. Because each can provide useful information, these views should be considered complementary rather than mutually exclusive ways to conceptualize brain organization for language. After discussing both perspectives, we determine the generalizations about language that can be made regardless of the viewpoint taken. In this section, we focus mainly on spoken language, saving our discussion of written language for later in the chapter.

Classic Neurological Conceptions

As we mentioned, the two men discussed in the opening vignette of the chapter, Bill and Jim, had a type of aphasia similar to that experienced by Broca’s patients. If you reread what the two men said, you may be struck by certain characteristics. You may have noticed the paucity of speech output: people with Broca’s aphasia have great difficulty

producing words. Broca deduced that the deficit he observed in his patients was specifically linguistic in nature because their difficulty with speech output was not accompanied by motoric problems of the vocal musculature, such as paralysis. The patients could utter sounds, albeit not linguistic ones, and were sometimes able to use the mouth and lips to perform orofacial movements, such as blowing out candles. Because the deficit appeared to be limited to the language domain, Broca conceptualized the region of the brain that now bears his name as the area that is critical for programming speech output.

Although difficulty in speech output is a glaring symptom of Broca's aphasia, you may have noticed other characteristics from Bill's and Jim's dialogue as well. For instance, the sentences do not fit a standard structure, but seem more like a telegram or text message (e.g., "Need help, send money"). This characteristic is often referred to as **telegraphic speech** because the words produced tend to be only content words, such as nouns and verbs. Function words and word endings are missing. Conjunctions (e.g., but, and) and prepositions (e.g., around, behind, about) are examples of function words that are missing from the speech of patients like Bill and Jim. Function words are important for speech comprehension because they provide information about the relations among words. Word endings also convey meaning that is important for language comprehension. For example, -ing appended to the end of a word designates an action that is happening at the present time.

Until this point, we have not discussed the specific location of the lesion that causes Broca's aphasia other than to say that it is in the left hemisphere. However, the knowledge we have gained in the previous chapters should enable us to make a well-educated guess as to its general location. First, guess whether the lesion is located anterior or posterior to the central fissure. Here's a hint: Remember that the most prominent behavioral deficit in Broca's aphasia is a disruption of speech output with relatively spared comprehension. Given that hint, you can reason that the lesion causing Broca's aphasia is anterior to the central fissure, because anterior regions are

specialized for motor output. Now, decide whether the lesion is mainly to the motor strip. You should conclude that it is not, because Broca's aphasia is not a result of facial or vocal muscle paralysis. Finally, consider whether the lesion causing Broca's aphasia is located ventrally or dorsally in the frontal lobe. This decision is more difficult, but if you remember the organization of the motor strip, you might be inclined to choose ventral, because the head and the face are represented at the inferior portion of the motor strip. In fact, the lesion that typically causes Broca's aphasia is in the frontal region, centered just anterior to the section of the motor strip that is responsible for control of the face (see [Figure 8.1](#)).

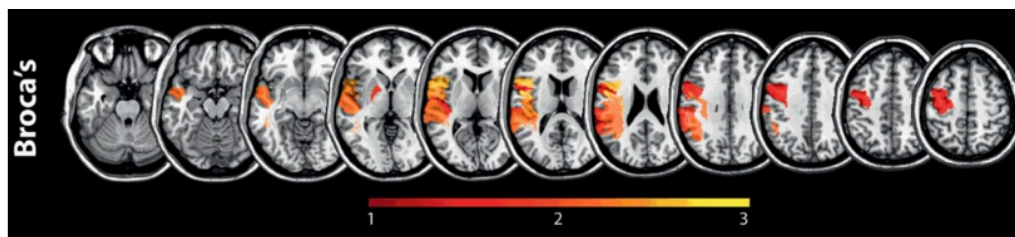


Figure 8.1 Site of damage associated with Broca's aphasia.

Shown here is a map indicating in red to yellow color those brain regions that, when damaged, are found to be specifically associated with Broca's aphasia compared to other types of aphasia. Yellow indicates areas of the brain that when damaged are particularly likely to produce this type of aphasia.

(from Yourganov et al., [2015](#))

An intriguing anatomical neuroimaging analysis of two of the original patients seen by Broca has yielded additional clues about the role of subcortical and cortical regions involved in Broca's aphasia (Dronkers et al., [2007](#)). Analysis of other patients suggested that when damage is limited to Broca's area alone, speech difficulties tend to be transient. Rather, the lesion that produces full-blown Broca's aphasia typically also involves surrounding white matter and subcortical connections (Mohr et al., [1978](#)). Because of these findings, researchers recently went back to the Musée Dupuytren in Paris, France, where the intact brains of two of Broca's patients have been stored for

more than a century (see [Figure 8.2](#)). Researchers carefully took the brains and put them in an MR scanner to discern the exact extent of the lesions. This analysis revealed that the lesions involved not only Broca's area on the lateral surface of the brain, but also more medial regions, including nearby white matter (Dronkers et al., [2007](#)). For those interested in the history of science, this paper also provides a fascinating discussion of the symptoms of these patients and Broca's original interpretation of his findings.

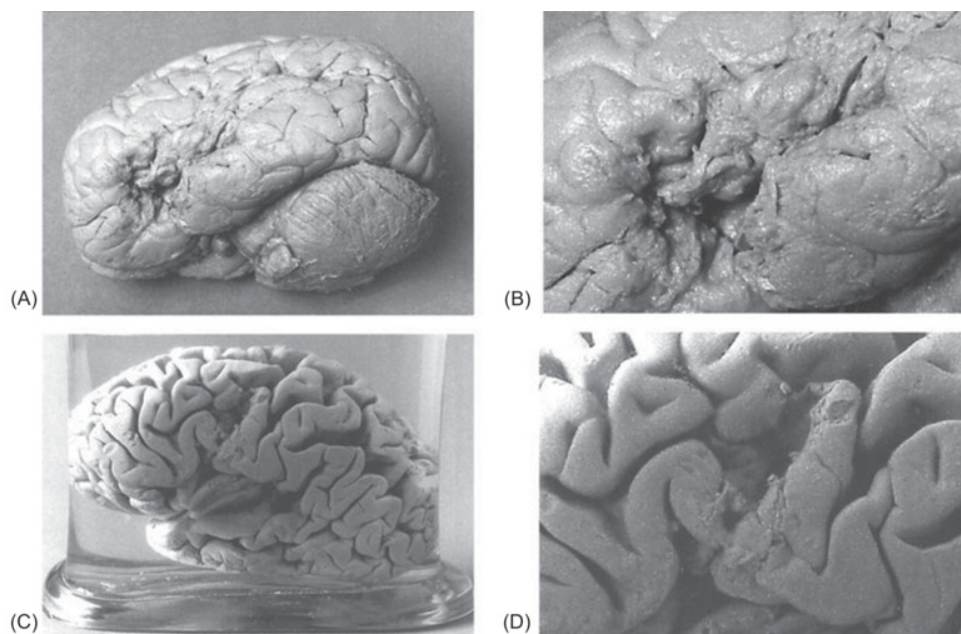


Figure 8.2 A lateral view of the brains of two of Broca's first two patients.

The brain of Broca's first patient, Leborgne, is shown in the top row (A, B); that of his second patient, Lelong, is shown in the bottom row (C, D). The left column shows the position of the lesion in the context of the whole brain (A, C), whereas the right-hand column shows the lesion in more detail (B, D). Notice that the lesion in Leborgne's brain encompassed not only Broca's area, but also surrounding tissue on the lateral surface. In contrast, the lesion in Lelong's brain was limited to the posterior section of Broca's area. Neuroimaging on these brains indicates that the lesion in both cases extended into adjacent medial areas, including the white matter.

(from Dronkers et al., [2007](#))

About 10 years after Broca characterized his aphasia, Karl Wernicke described the converse syndrome – disrupted speech comprehension along with fluent (but nonsensical) speech output – which became known as [Wernicke's aphasia](#). Fluent is the operative word in describing this syndrome, because speech output occurs without hesitation, sounds are well formed, and all parts of speech are present. Yet, what these patients say makes little sense; their output is a jumble of words, often referred to as a word salad. In fact, the speech of a person with Wernicke's aphasia can be so disjointed that someone without proper training in a medically relevant field might be tempted to refer the person to a psychiatrist rather than a neurologist.

Following is an example of speech from a 70-year-old man who acquired Wernicke's aphasia after blockage of part of his middle cerebral artery. Unlike the speech of patients with Broca's aphasia, his speech was produced at a normal rate and rhythm and with an intonational pattern that was, if anything, exaggerated: "I feel very well. My hearing, writing been doing well, things that I couldn't hear from. In other words, I used to be able to work cigarettes I don't know how This year the last three years, or perhaps a little more, I didn't know how to do me any able to" (Goodglass, [1976](#), p. 239).

The speech of people with Wernicke's aphasia is hard to comprehend not only because the words are combined in a way that makes little sense, but also because of errors in producing specific words, known as [paraphasias](#). Paraphasias manifest in numerous forms. In a [semantic paraphasia](#), the substituted word has a meaning similar to the intended word (e.g., substitution of "barn" for "house"). In a [phonemic paraphasia](#), the substituted word has a sound similar to the intended word (e.g., "table" becomes "trable" or "fable"). On other occasions, people with Wernicke's aphasia produce sounds known as [neologisms](#), which are made-up words that follow the rules for combining sounds in the language, yet are not real words (e.g., "galump," "trebbin").

Despite the fluency of their output, people with Wernicke's aphasia generally have quite a lot of trouble understanding language. They may not even be able to understand enough to follow simple commands such as "Point to the blue square" or "Pick up the spoon." Wernicke originally postulated that these people cannot link the "sound images" of language to meaning.

From what we just learned about the behavioral manifestations of Wernicke's aphasia, you should be able to make an educated guess as to the location of the lesion that typically results in this disorder. Is the lesion anterior to or posterior to the central fissure? You should have guessed posterior, because those regions of the brain are involved in interpreting sensory information. But where in posterior cortex? Consider that Wernicke described this aphasia as an inability to link a sound image to meaning or stored information. What posterior brain regions might that bring to mind? Because we are discussing a sound image, you might consider regions in the superior temporal lobe near Heschl's gyrus, which is the primary auditory area. Because the retrieval of meaning is important, other regions of the temporal lobe might be considered plausible candidates. Finally, because, as we learned in [Chapter 1](#), the parietal lobe makes linkages across modalities and representations, it might be a viable candidate for translating a sensory input to meaning. As you can see in [Figure 8.3](#), the lesion that typically causes Wernicke's aphasia is close to all these areas; it is typically situated at the junction of the temporal lobe with parietal and occipital regions, near Heschl's gyrus.

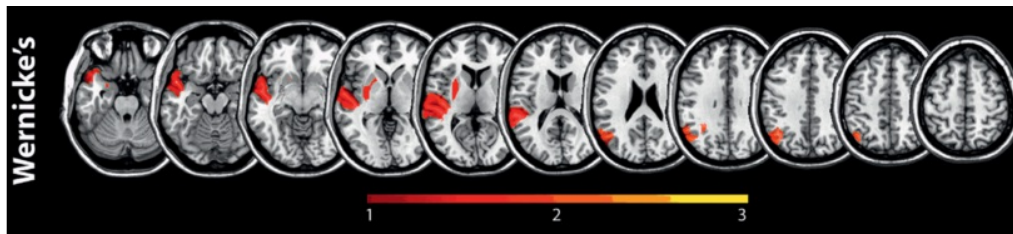


Figure 8.3 Site of damage associated with Wernicke's aphasia.

Shown here is a map indicating in color those brain regions that, when damaged, are found to be specifically associated with Wernicke's aphasia compared to other types of aphasia. Note how those these regions are more posterior to those associated with Broca's aphasia.

(from Yourganov et al., [2015](#))

While both Broca and Wernicke made astute observations, subsequent work has shown that the behavioral syndromes that Broca and Wernicke described are caused by lesions to brain areas a bit distinct from the area that they proposed as being critical. Although it is true that Broca's and Wernicke's areas are typically damaged in Broca's and Wernicke's aphasias, respectively, damage to these regions alone is not sufficient to cause the aphasic syndrome. For example, the lesion that causes Wernicke's aphasia typically includes Wernicke's area as well as surrounding tissue. Likewise, to produce Broca's aphasia, a lesion must include Broca's area but also damage to surrounding areas, most notably the underlying white matter. And, in at least some cases, an aphasic syndrome (e.g., Wernicke's aphasia) may be observed even if damage does not specifically include the region after which it is named (e.g., Wernicke's area) (Dronkers, [2000](#)).

At this point you may be a bit confused wondering exactly what is the difference between lesions that cause Broca's compared to Wernicke's aphasia. The crucial distinction is between aphasic symptoms that are observed after anterior lesions versus those observed after posterior lesions of the left hemisphere, regardless of whether Broca's or Wernicke's areas are specifically damaged.

Not only did Wernicke discover the aphasia that bears his name, but he also postulated and documented the existence of other aphasic syndromes. Wernicke assumed a basic blueprint for the neurological organization of language in which Broca's area is responsible for speech output and Wernicke's area is responsible for speech comprehension. He went on to suggest that damage severing the connection between these two areas should also result in yet another aphasic syndrome. He reasoned that language comprehension should be intact because Wernicke's area is intact and that speech production should be fluent because Broca's area would be intact. Yet the person's output would be characterized by paraphasias and difficulty in repeating what has just been heard. This difficulty would arise because the sound images of language, for which Wernicke's area is responsible, cannot be conducted forward to Broca's area, which is responsible for speech output. This syndrome has come to be known as [conduction aphasia](#).

You may remember from [Chapter 2](#) that syndromes caused by severed connections between intact brain regions are called [disconnection syndromes](#). Conduction aphasia is a good example of a disconnection syndrome, because the behavioral dysfunction does not arise from damage to either the brain region that processes the sound image (Wernicke's area) or the region of the brain that produces the speech output (Broca's area); instead, the deficit arises from an inability to relay information from one intact area to another intact area. It is as if a communication cable between the two regions were broken. In fact, a large nerve fiber tract, known as the arcuate fasciculus, connects these two regions, and part of this tract is often damaged in conduction aphasia, along with surrounding tissue (see Catani and Mesulam, [2008](#), for historical insights and a current-day examination of this nerve fiber tract) (see [Figure 8.4](#)).

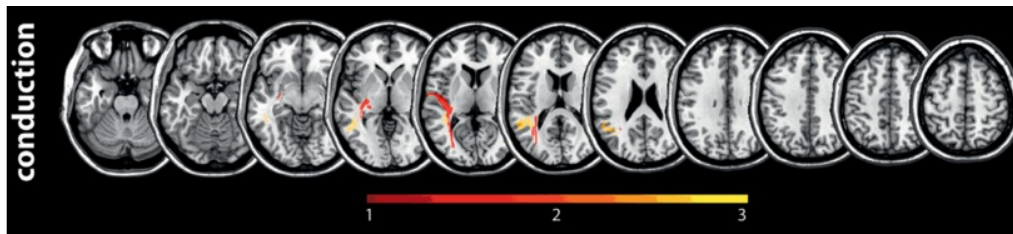


Figure 8.4 Site of damage associated with conduction aphasia.

Shown here is a map indicating in color those brain regions that, when damaged, are found to be specifically associated with conduction aphasia compared to other types of aphasia. Note how the lesions are mainly to white matter in regions between Wernicke's and Broca's area.

(from Yourganov et al., [2015](#))

Finally, the aphasiologists speculated that people who had extensive damage to multiple parts of the system (e.g., the output center and the sound image center) would be left with neither the ability to comprehend language nor the ability to produce it. Behaviorally, such a syndrome has been observed, [global aphasia](#). This syndrome is associated with extensive left-hemisphere damage that typically includes not only Wernicke's and Broca's areas, but the area between them as well (see [Figure 8.5](#)).

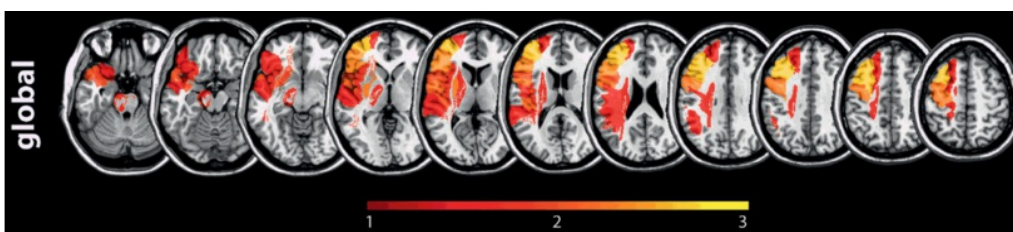


Figure 8.5 Site of damage associated with global aphasia.

Shown here is a map indicating in red to yellow color those brain regions that, when damaged, are found to be specifically associated with global aphasia compared to other types of aphasia. Yellow indicates areas of the brain that when damaged are particularly likely to produce this type of aphasia. Notice how the regions associated with this type of aphasia span both anterior and posterior regions of the left hemisphere.

(from Yourganov et al., [2015](#))

[Table 8.2](#) lists the major aphasic syndromes observed clinically and their characteristics. Because different nomenclatures are used for these various syndromes, you may also find Broca's aphasia referred to as nonfluent, agrammatic, or anterior aphasia, whereas Wernicke's aphasia is also sometimes referred to as fluent, or posterior, aphasia. (For a review of contemporary perspectives on aphasia, see Tippet et al., [2014](#)).

Table 8.2 Basic Characteristics of the Major Aphasic Syndromes

| TYPE OF APHASIA | SPONTANEOUS SPEECH | PARAPHASIA | COMPREHENSION | REPETITION |
|--------------------|-----------------------|---------------------|---------------|------------|
| Broca's | Nonfluent | Uncommon | Good | Poor |
| Wernicke's | Fluent | Common (verbal) | Poor | Poor |
| Conduction | Fluent | Common (literal) | Good | Poor |
| Global | Nonfluent | Variable | Poor | Poor |

Although it provides a useful organizing framework, the three-part model of nineteenth-century aphasiologists (with the brain containing a language input center, a language output center, and a critical neural pathway connecting the two) does not adequately explain all the symptoms of aphasia. The primary difficulty is that the model presents an oversimplified view of language deficits following brain damage. For example, the model posits that Broca's aphasia is caused by damage to the language-output center. However, as we will see, the difficulties experienced by patients with Broca's aphasia are not limited to speech output. In the [next section](#), we further explore the complexity of aphasic symptoms from a psycholinguistic perspective.

Psycholinguistic Perspectives

In more recent decades, psychologists and psycholinguists have studied aphasic disorders as a window for uncovering the mental structure for language (Hillis, [2007](#)). Psycholinguists have traditionally divided language into three main components: phonology, syntax, and semantics. Roughly speaking, [phonology](#) examines the sounds that compose a language and the rules that govern their combination, [syntax](#) is the rules of grammar, and [semantics](#) is the meaning of language. In the subsequent sections, we discuss how each of these components of language is affected by aphasic syndromes.

Phonology

Phonology refers to the rules governing the sounds of language. Linguists have conceptualized two ways of representing the sounds of speech: phonemically and phonetically. A phoneme is considered the smallest unit of sound that can signal meaning. For example, /b/ and /p/ mean nothing by themselves (/ / is used to symbolize a linguistic sound, allowing, for example, the sound /b/ to be differentiated from the letter b), but they nonetheless cause /bat/ and /pat/ to have different meanings. In contrast, the phonetic representation of a speech sound describes how it is produced on particular occasions or in particular contexts. For example, the /p/ in pill is aspirated (produced with a burst of air), whereas the /p/ in spill is not aspirated.

People with Broca's aphasia, and others with aphasia whose speech is nonfluent, have difficulty producing the correct variant of a phoneme (Blumstein, [1991](#)). In other words, they cannot produce the correct phonetic representation of a speech sound. The production of different variants of the same phoneme requires precise control over the articulatory muscles, with each version varying in subtle but important ways. This precision is lacking in people who have Broca's aphasia.

In contrast, patients with Wernicke's aphasia (and other fluent aphasias) do not have difficulty producing the correct variant of a given phoneme. However, they often have difficulty producing the correct phoneme, for example mistakenly saying "pat" for

“bat.” This dissociation suggests that the phonemic representation of a speech sound is distinct from its phonetic representation. Patients with Broca’s aphasia appear to have difficulty producing both the correct phonetic and the correct phonemic representations of a speech sound, whereas those with Wernicke’s aphasia have difficulty only with phonemic representations.

The disruption of the phonemic representation of a speech sound in aphasia can be well explained by a psycholinguistic perspective that considers speech sounds as being composed of a set of distinctive features. According to linguistic theory, consonants vary in distinctive features, two of which are place of articulation and voicing. Both of these features describe the voyage of air from the lungs out through the vocal tract. **Place of articulation** describes the location in the vocal tract where airflow is obstructed. For example, /b/ and /p/ are known as labial stops because obstruction occurs at the lips; /d/ and /t/ are alveolar stops because the obstruction occurs from tongue placement at the alveolar ridge behind the front teeth; and /g/ and /k/ are velar stops because the air is obstructed at the velar, or soft, palate in the back of the mouth. Say these sounds to yourself right now and it will become obvious how the airflow is obstructed in different places. **Voicing** describes the timing between the release of the air for the stop consonant and the vibration of the vocal cords. When a consonant is voiced, the release of air and the vibration of the vocal cords coincide (/b/, /d/, /g/), whereas in an unvoiced consonant (/p/, /t/, /k/), the vocal cords do not begin to vibrate until after the release. The only difference between a /b/ and a /p/, which are both labial stops, is that vocal-cord vibration and air release are coincident in time for a /b/, whereas for a /p/ the air release precedes vocal-cord vibration by a mere 40 to 80 ms! (Perhaps you’ll appreciate the precision of your brain a bit more the next time you utter or hear a sentence like “Pat, it’s your turn to bat.”)

The distinctive features of a phoneme influence the production errors of aphasic patients, as well as some of their receptive difficulties. When making phonemic errors, aphasics (regardless of the type of aphasia) are much more likely to substitute a sound

that differs in only one distinctive feature (e.g., /b/ for /p/, which differ only in voicing) rather than two (e.g., /b/ for /t/, which differ in both voicing and place of articulation) (Blumstein, [1991](#)). Most people with aphasia exhibit some problems in perceptually discerning these features as well as in producing them (e.g., Miceli et al., [1980](#)). Not all distinctive features have equal saliency, though, because some may be less resistant to confusion than others. For example, errors based on place of articulation (e.g., /pa/ versus /ta/) are more common than errors based on voicing (e.g., /pa/ versus /ba/) (e.g., Baker et al., [1981](#)). In addition, deficits in being able to perform phonological analysis on speech may influence comprehension in Wernicke's aphasics (Robson et al., [2012](#)).

Phonological theory describes not only the sounds of language, but also the rules by which sounds can be combined. So, for example, in English a valid combination of sounds would be "casmeck," whereas an invalid combination would be "cnamzik." As you may remember from our earlier discussion, patients with aphasia, most notably Wernicke's aphasics, often construct novel series of sounds called neologisms. These neologisms could be words, because they follow the rules for combining sounds, but the particular combination used does not constitute an actual word in the language. In this sense, people with aphasia appear to respect the rules of phonology for the language that they speak.

In summary, phonologic processing can be disrupted in aphasia in two major ways. First, phonetic representations of phonemes are often disrupted in patients with nonfluent (Broca's) aphasias, but remain intact in patients with fluent (Wernicke's) aphasias. Second, phoneme substitution in production and difficulty in phoneme discrimination are common in both fluent and nonfluent aphasias and appear to be governed by the similarity of phonemes to each other along the dimensions of distinctive contrasts. Analysis of language breakdown in aphasia suggests that the phonetic and phonemic representations of sounds are distinct, in that the phonemic representation may be compromised even when the phonetic representation is intact. Despite these

difficulties, the rules that govern the combination of specific phonemes are preserved in aphasic speech.

Syntax

The second fundamental component of language, syntax, describes the rules governing how words are put together in sentences. For example, in English we generally use a subject-verb-object (SVO) word order, as in the sentence “The cat sat on her lap.” In some other languages, such as Turkish, the standard word order is subject-object-verb (SOV). Within a language, various syntactic forms or frames are often allowed. SVO word order in English is considered the active voice, and OVS is considered the passive voice, as in the sentence “The robber [object] was chased [verb] by the police officer [subject].”

People with certain types of aphasia, most notably those with anterior lesions, often have difficulties with the syntactic aspects of language processing (Caramazza and Zurif, [1976](#); Caramazza et al., [1981](#)). In the opening vignette, function words and word endings are missing from the men’s speech, and the words are not structured in a standard syntactic frame. Historically, researchers assumed that people with anterior aphasia failed to produce function words and prepositions not because they had difficulties with syntax, but because they found it so hard to produce speech, so they carefully chose those words that would convey the most meaning for the least effort – that is, nouns and verbs. However, people with anterior aphasia have a compromised ability both to produce and to comprehend the grammatical aspects of language. Therefore, anterior aphasia is sometimes called [agrammatic aphasia](#).

For example, because of their relative insensitivity to syntactic markers, people with anterior aphasia assume an SVO word order for both the active sentence “The cat chased the kitten” and the passive sentence “The cat was chased by the kitten.” They ignore the grammatical markers of the auxiliary verb was and the preposition by as signaling the nonstandard OVS (object-verb-subject) word order. As a result, when

asked to select a picture representing the meaning of each sentence, these aphasics select the same picture for both sentences, one of an adult feline chasing an immature feline.

These difficulties in syntax are observed consistently even across different languages with varying grammatical markers. For example, in English, we have only one definite article, the, but in other languages, the for a noun that is the subject of the sentence may differ from the for a noun that is the object. In German, the for male nouns that are the subject of the sentence is der, whereas when a male noun is the object of a sentence, the becomes den and an -n is added to the end of the noun. The sentence “Der Junge küsste das Mädchen” means “The boy kissed the girl,” whereas “Den Jungen küsste das Mädchen” means “The girl kissed the boy.” The den and the -n at the end of Junge indicate that the boy is playing the role of the object. Given these two sentences, German-speaking people with anterior aphasia will have difficulty realizing that the boy is being kissed in the second sentence, because they are insensitive to the grammatical markers that signal the less typical grammatical construction (von Stockert and Bader, [1976](#)).

Despite having problems differentiating between different syntactic constructions, patients with anterior aphasia have little trouble understanding sentences such as “The ice-cream cone was eaten by the boy,” because their ability to understand the meaning of words (i.e., semantics) limits the interpretation of such sentences. A person with anterior aphasia knows that ice-cream cones cannot eat boys (except, perhaps, in some very bizarre horror movie) and therefore is not confused by the OVS word order.

Knowledge of syntax appears to be spared in people with posterior aphasia, in contrast to those with anterior aphasia, who are more likely to have deficits in this area. As mentioned at the beginning of this chapter, speech in posterior aphasia is fluent and contains all the grammatical markers (e.g., verb endings, prepositions, auxiliary verbs) that would normally be found in intact speech production, although the sentences produced are largely devoid of meaning.

Semantics

The third fundamental component of language, semantics, is concerned with the meaning of words and word combinations. Sentences may have different syntactic structures yet have approximately the same meaning. For example, “The beaver appeared among the reeds on the far side of the lake from where I was standing” has the same basic meaning as “On the side of the lake opposite from where I was positioned, the beaver appeared among the reeds.”

The ability to extract meaning from language or to use words to produce meaning is seriously compromised in patients with posterior aphasia. In severe cases, such patients may not understand even simple commands such as “Point to the blue circle” and “Point to the big red square,” which are included in a quick screening device for aphasia known as the Token Test (De Renzi, [1980](#)). In less severe cases, the patients understand simple nouns but have difficulty comprehending more complicated linguistic material. Furthermore, this difficulty in comprehending the meaning of language is pervasive across modalities, extending to both auditory and written language, and in some cases to the nonverbal domain as well (De Renzi et al., [1972](#)). This finding indicates that the meaning system itself, rather than some modality-specific (e.g., auditory) access to that system, is disrupted. Posterior aphasics read and write no better than they can understand speech, and their speech output conveys no more meaning than they appear to extract from spoken language.

In contrast, patients with anterior aphasia appear to have intact semantic processing. They can usually follow simple commands with ease, although, as mentioned previously, they might exhibit minor problems in comprehension when syntax plays a large role in interpreting sentences. For example, if told, “Place the blue circle on top of the big red square,” patients with anterior aphasia might react by putting the blue circle next to the big red square. Their problems with syntax hinder their ability to comprehend the prepositional phrase that describes the desired relationship between the two items.

To summarize, the disruption of language processing observed in aphasia syndromes suggests that they can indeed be fruitfully understood through the lens of psycholinguistics. As shown in [Table 8.3](#), the pattern of language components disrupted by anterior lesions of the left hemisphere differs from that observed after posterior lesions to the left hemisphere.

Table 8.3 Characteristics of the Major Aphasic Syndromes from a Psycholinguistic Perspective

| TYPE OF APHASIA | Phonetics | Phonemics | Syntax | Semantics |
|---------------------------|------------------|------------------|---------------|------------------|
| Anterior (Broca's) | Affected | Affected | Affected | Intact |
| Posterior (Wernicke's) | Intact | Affected | Intact | Affected |

Evidence From Double Dissociations

The models we have just discussed conceptualize the difference between anterior and posterior aphasias in two quite distinct manners. On the one hand, one model views anterior areas as important for speech output and posterior areas as important for speech comprehension. On the other hand, the other model argues that anterior areas are important for syntactic processing and that posterior areas are involved in semantic processing. Nonetheless, regardless of how the deficits in the two types of aphasias are distinguished (input-output or syntactic-semantic), these syndromes represent a double dissociation in language processing.

On a theoretical level, these dissociations tell us that no unitary language center or language system exists in the brain. Rather, the system has specific components that can act more or less independently of one another. This knowledge is important both for more complete understanding of the neural control of language and for practical reasons.

Because the input and output of auditory language are governed by somewhat different systems, therapies geared toward speech production are likely to have little effect on comprehension. Likewise, because the grammar and meaning of a language appear to be under separate neural control, being tutored in the rules of grammar is unlikely to aid a person with aphasia who is having difficulty producing meaningful sentences.

While these dissociations are based on research with clinical populations dating back over 100 years, how well do they hold up to the explosion of research using neuroimaging and electrophysiological techniques in the past 20 years? In general, research using these newer methods has corroborated these dichotomies in their broad outline. Anterior and posterior regions of the left hemisphere show activation under different circumstances. Activity in the superior temporal regions of the left hemisphere, which Wernicke described as processing sound images of words, is observed when people must distinguish aurally presented words from aurally presented nonwords (e.g., Frith et al., [1991](#)). In contrast, Broca's area, which is implicated in speech production, becomes active when words must be repeated rather than just heard (Petersen et al., [1988](#)).

Imaging studies using fMRI support the idea that anterior regions of the left hemisphere are involved in processing syntax, while posterior temporal regions are important for semantics (Stromswold et al., [1996](#); Price et al., [1997](#); Price, [1998](#)). And ERP components can be distinguished by their sensitivity to semantic versus syntactic processing. As you may remember from [Chapter 3](#), a specific ERP component, the N400, is elicited when a word, either visual or auditory, in a sentence violates semantic expectation, such as "He spread the warm bread with socks" or "The girl dropped the sky on the table." As shown in [Figure 8.6A](#), this component tends to be larger over the left hemisphere than the right (Hagoort and Brown, [2000a](#)), consistent with recordings from patients with brain damage, intracranial recordings, and magnetoencephalographic data, which suggests that this effect reflects activity in the left temporal lobe (Van Petten and Luka, [2006](#)).

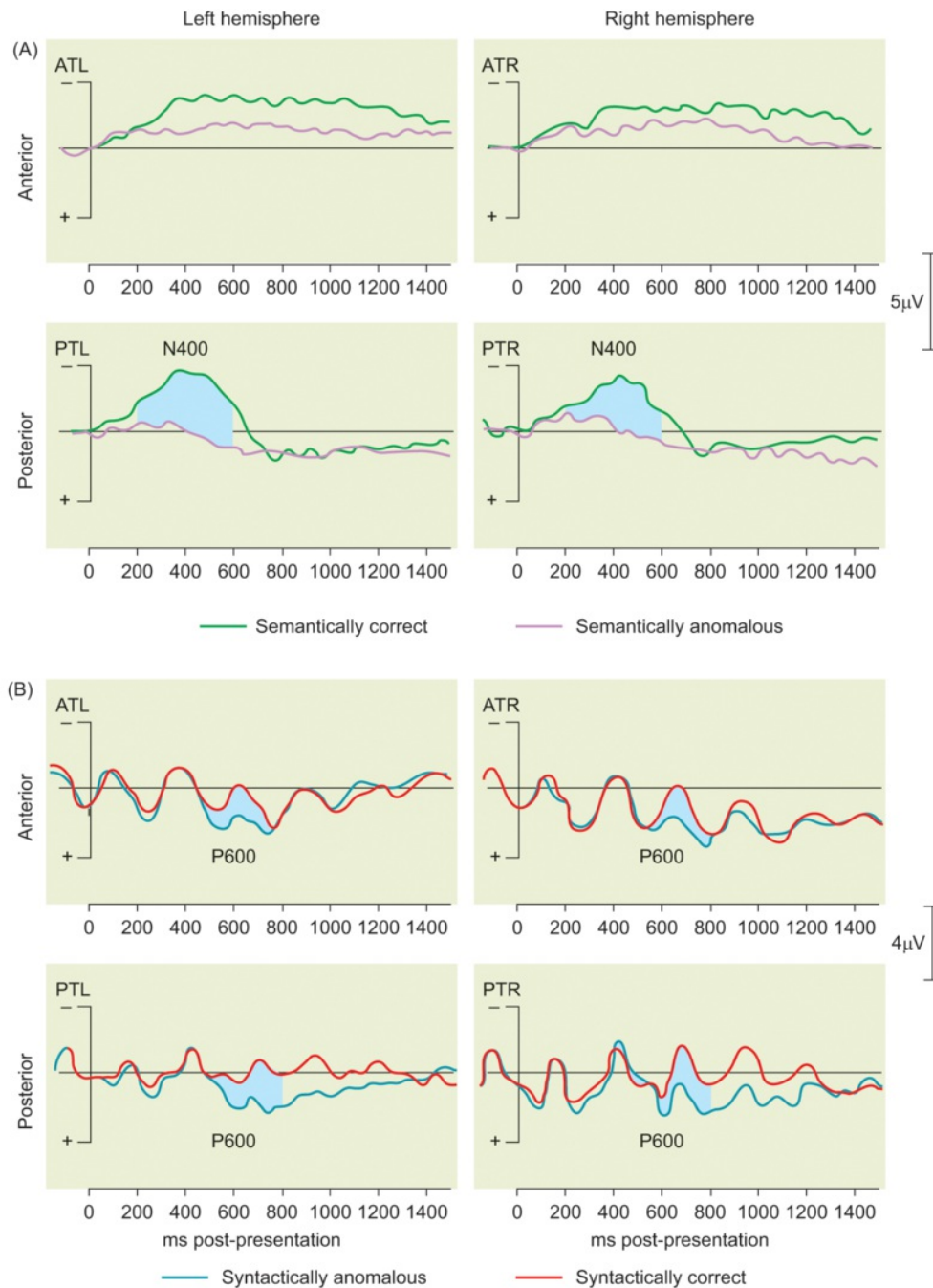


Figure 8.6 ERP components sensitive to aspects of language processing.

(A) Shown here is the N400 (indicated by shading) that occurs in response to semantically anomalous material in the auditory modality. Notice that it is larger over posterior regions of the brain than anterior regions and larger over the left hemisphere than the right. (B) Shown here is the P600 (indicated by shading) that occurs in response to syntactically anomalous sentences. Notice that, unlike the N400, it is observed over both anterior and posterior regions.

In contrast, a different component is elicited when words occur that render a sentence ungrammatical, such as “The spoiled child throw the toys on the floor.” This component, the P600 (also sometimes referred to as the SPS, for syntactic positive shift), is observed both over posterior and anterior recording sites, as shown in [Figure 8.6B](#). Because it has been observed across a variety of languages, such as German, English, and Dutch, the P600 is known to be sensitive to syntax regardless of the particulars of a given language system (Friederici et al., [1996](#); Osterhout and Holcomb, [1992](#); Hagoort and Brown, [2000b](#)).

Although these studies provide converging evidence in support of basic components of language as identified by aphasiologists, more recent research, which we discuss next, has provided additional insights that underscore the need to step beyond traditional models of language processing in the brain.

Language Processing From a Network Perspective

While dichotomies – such as those between comprehension and production, or between syntax and semantics– provide useful heuristics, they really just scratch the surface of the complexity of language processing. As users of language, we generally are not concerned with “syntax” or “semantics” nor “input” and “output.” We care about comprehending language in its many forms, auditory and visual, and in producing language output that is comprehensible to others, either in speech or written language. Language provides us with a unique and amazingly effective tool for communication. As such, more recent research drawn from neuroimaging and other methods has emphasized how both anterior and posterior regions of the brain work together to meet such goals. At the end of this section, we propose a more integrative, systems-based approach to the understanding of language processing in the human brain, as an expansion to the model proposed by aphasiologists and psycholinguists.

In general, three major insights about language have been provided by recent studies of language processing. The first has been to provide more specific information about

the localization of brain tissue that is active when people are engaged in language-related processing. In general, these studies indicate that activation extends well beyond those regions traditionally considered “language” areas (e.g., Broca’s and Wernicke’s areas) even including the right hemisphere as well (Price, [2012](#)), and that areas considered “language-specific” may actually process other types of information as well. The second insight is that the language subsystems are not as distinct as we initially supposed. Rather, the neural organization for processing phonology, syntax, and semantics shows some degree of overlap. Part of this overlap may occur because different components of language rely on domain-general computations that are required by both, say, syntax and semantics. The third important insight is that language appears to be supported by interactions between brain regions that are reliant on the white-matter connectivity between them.

Reduced Evidence for Language-Dedicated Regions

Recent studies have provided a more complicated map of the cortical anatomy underlying language processing. The classic model had specific language functions neatly compartmentalized to specific pieces of neural tissue. For example, the classical viewpoint was that the posterior region of the superior temporal gyrus is specialized for processing language-related sounds. Yet a variety of work suggests that this may not be the case. Neuroimaging evidence indicates that these left-hemisphere regions process more than just speech sounds and the processing of speech sounds may extend beyond these classic areas. How are we to make sense of these findings and what type of processing are these regions doing?

Researchers have suggested that to understand how the brain processes speech input we need to consider in more depth the types of computations that are performed on the incoming acoustic stream. Some research has emphasized that this sound stream can be chunked into different time bins: interpreting informational cues requires the integration of acoustic information over about 500–2,000 milliseconds, while syllabic information

lasts about 150–300 milliseconds, and, as we learned earlier, specific acoustic features, such as voicing, occur on an even smaller scale: 20–80 milliseconds. One model suggests that such information is processed in parallel with distinct neural oscillations tracking information in each of these different time bins (Poeppel, [2014](#)), allowing for parallel processing of both linguistic and nonlinguistic sounds by both hemispheres. Such a system would allow a specialization of the left hemisphere for speech information if its mechanisms are biased toward processing information that occurs over shorter rather than longer time scales (Poeppel, [2003](#)).

Other viewpoints argue that superior temporal regions of the left hemisphere are particularly adept at processing acoustic information that occurs not in short time frames, but rather with fast temporal transitions. In contrast, the right hemisphere may be more adept at processing spectral information, that is, the distribution of information with regards to frequency (Zatorre and Gandour, [2008](#)). Still another viewpoint suggests that the emphasis on discerning which acoustic features lead to left-hemisphere specialization for the processing of linguistic information is misguided, as actually lateralization of processing for nonspeech sounds in the right hemisphere is stronger than lateralization for speech sounds to the left hemisphere. This viewpoint argues that perhaps more domain-general acoustic features, such as duration and frequency, do drive right-hemisphere processing of sounds, while left-hemisphere processing of speech is not driven by acoustic factors, but rather is related to the linguistic status of information in some, as of yet, undetermined manner (McGettigan and Scott, [2012](#)). Obviously, this issue remains one of ongoing debate. Nonetheless, all of these viewpoints emphasize that rather than the processing of speech relying on a specific region of the brain, distinct types and streams of information contained in speech are likely to be processed in parallel across the brain whether it be through separate bands of neural oscillations or in parallel across the hemispheres.

Overlap of Syntactic, Semantic, and Phonological Processing

Although we have treated syntax, semantics, and phonology as distinct and separable systems, they are likely to have some degree of overlap, and the degree of overlap may depend on the demands of a particular linguistic situation. According to classic psycholinguistic theory, one first builds a syntactic frame (e.g., subject-verb-object) and then drops the appropriate semantic values into that frame (e.g., “The dog bit the mailman”). According to the traditional view, not only are syntax and semantics separable, but syntax also precedes semantics. Results from event-related potential studies of language processing suggest otherwise. Remember, as we discussed earlier, an N400 is elicited when a word in a sentence violates semantic expectation, whereas a P600 is elicited by words that render a sentence ungrammatical. If a syntactic frame is constructed and then words are dropped into it, we would expect that the following initial part of a sentence, “The hearty meal was devouring ...,” to elicit an N400, because it is impossible for meals to eat anything, and not to elicit a P600, as the grammatical structure of the noun phrase is perfectly reasonable (e.g., “The lion was devouring ...”). Yet this sentence does not produce an N400, but rather a large P600 (see [Figure 8.7](#); Kim and Osterhout, [2005](#)), while the sentence “The dusty tabletops were devouring ...” does produce an N400.

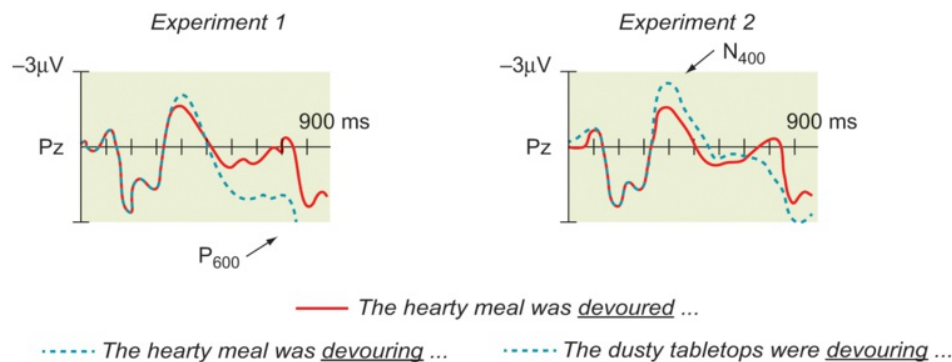


Figure 8.7 ERP evidence of the interaction between syntactic and semantic processing.

(Left) Here the semantically anomalous phrase “The hearty meal was devouring” does not elicit an N400 but rather a P600. (Right) In contrast, the semantic mismatch between “tabletops” and “devouring” elicits an N400. These findings are inconsistent with the idea that a syntactic frame for a sentence is constructed and then words with the appropriate semantic value are dropped into that frame. If that were the case, the sentence on the left should have elicited an N400 just like the sentence on the right.

How are we to understand these results? One way is to assume that syntax does not always precede semantics and that the language system does a quick first pass for semantic associations. Under such conditions, the words “meal” and “devouring” are appropriately related and therefore do not elicit an N400, whereas the lack of a semantic relationship between “tabletops” and “devouring” does. But when “meal” and “devouring” are detected to be syntactically anomalous given the semantics of the sentence, a P600 is emitted. This has led some researchers to suggest that the P600 is not a marker for syntax per se, but rather for the combination of semantic and syntactic processing (Kuperberg, [2007](#)), suggesting overlap between these two systems.

The idea that language involves overlapping rather than functionally independent systems is also supported by neuroimaging. Results from the neuroimaging literature indicate that left inferior prefrontal and premotor regions, traditionally thought to be involved in language production, become active in receptive language tasks, such as phonological discrimination, speech comprehension, and word reading (e.g., Kelley et

al., [1998](#); Fiez and Petersen, [1998](#)). For example, a joint TMS–PET study shows that activity in Broca’s area during speech perception predicts the size of the motor potentials observed at the lips in response to simultaneous TMS over primary motor cortex (Watkins and Paus, [2004](#)). This finding suggests that posterior processing of speech may prime “motor” regions involved in language even during comprehension.

The particular region of left prefrontal cortex activated during receptive language appears to depend on whether phonological or semantic processing is paramount. When an emphasis is placed on phonological processing, such as how a word sounds compared to how it looks (Fiez et al., [1995](#)), when a specific phoneme must be detected (e.g., /pa/), or when a decision about the final consonant in a word is required, activation is observed in Broca’s area in BA 44 (Zatorre et al., [1996](#)). In fact, these neuroimaging studies prompted researchers to go back and investigate more thoroughly how well the individuals with Broca’s aphasia process incoming phonological information, which traditionally was thought to be unaffected. When they did, they documented difficulty in processing a number of different aspects of phonology in such patients, such as problems in reading pronounceable nonwords (e.g., “lums”), which require the ability to link letters to their phonological representations (Fiez et al., [2006](#)).

When semantic rather than phonological processing of receptive language is emphasized, neuroimaging studies reveal activation in more anterior portions of the inferior frontal lobe (BA 45/47) (Wagner, [1999](#)). Consistent with this idea, anodal transcranial direct current stimulation, which is thought to facilitate neuronal processing, speeds the ability to make semantic judgments about words that have multiple meanings. For example, if shown the word “novel,” which could either refer to a book or to the idea that something is new and original, participants are faster to determine that it is indeed semantically related to a word such as “biography” (Ihara et al., [2015](#)).

This dissociation between the role of these two inferior frontal regions for phonological versus semantic processing has been confirmed by studies using TMS.

Stimulation over anterior regions of the left inferior frontal gyrus interferes with synonym judgments (e.g., do “gift” and “present” mean the same thing), but not with judgments about whether two words are homophones, that is, sound the same (e.g., “manner” and “manor”). Stimulation of posterior regions shows the opposite pattern: disruption of homophone judgments but not synonym judgments (Gough et al., [2005](#)) (see [Figure 8.8](#)).

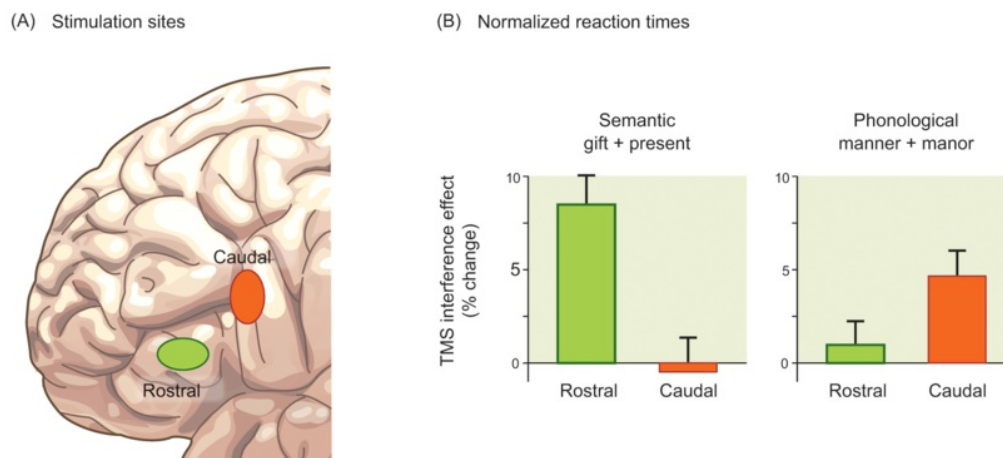


Figure 8.8 A dissociation between phonological and semantic processing in left inferior frontal regions as demonstrated by TMS.

(A) Shown here are the locations of stimulation with TMS for rostral (shown in green) versus caudal (shown in orange) portions of the inferior prefrontal cortex. (B) (left) Rostral stimulation but not caudal stimulation increases reaction time for semantic judgments. (right) In contrast, caudal stimulation but not rostral stimulation increases reaction time for phonological judgments.

(from Devlin and Watkins, [2007](#))

What are we to make of the idea that these “language production” regions are involved in phonological and semantic aspects of receptive language tasks? Is the classical model all wrong? Probably not; it just needs some refinement. The consensus is that indeed long-term storage of phonological and semantic knowledge is dependent on posterior regions. Frontal regions, in contrast, appear to be involved in the short-

term maintenance and strategic control over phonological and semantic information. In doing so, these frontal regions may aid language comprehension.

As we will discuss in Chapter 11 (see page [343](#)), lateral prefrontal regions help to implement executive processes that allow information in working memory to be reordered, manipulated, or considered in relation to other relevant information. These executive processes may be required to allow for comprehension. Consider the case of “garden path” sentences. In such sentences, you are led down the path to an initial interpretation, which then must be revised. To reach the correct interpretation of the sentence’s meaning, the relationship between words that you have been holding on-line in working memory must be reconsidered. Take for example, the sentence “While the man coached the woman stayed at home.” When you first read the sentence you may have thought that the man was coaching the woman. Only as you got further along in the sentence did you realize that at the time he was coaching, the woman was staying at home. The information you retained in working memory must now be conceptually reordered for the meaning, that is, the semantics, of the sentence to be understood. Patients with left inferior frontal lobe damage have particular trouble doing so (Vuong and Martin, [2015](#)). In this manner, frontal regions can aid not only in language production but language comprehension as well.

It is important to realize that these executive processes implemented by lateral prefrontal regions are domain-general, that is, they are applied to all types of information in working memory, not just linguistic information. For example, in one study, people heard or saw sequences of items and had to make comparisons among them, requiring working memory. Some of the judgments were linguistic, requiring people to determine whether two consonants were the same or whether two words rhymed. Other judgments required comparison of single tones or false fonts. Inferior frontal regions were activated across all tasks, suggesting that this region may play a role in aspects of working memory processes that must be applied when incoming information must be compared or categorized regardless of whether it is linguistic or

not (Burton et al., [2005](#)). Findings such as these, as well as those from patients with brain damage, have led some researchers to suggest that, in fact, these left inferior frontal regions are not really specialized for syntax per se, but rather are part of an extended brain network that helps to perform syntactic processing (Tyler et al., [2011](#)). In the [next section](#) we talk a bit more about the potential organization of such extended networks.

Interacting Brain Regions Enable Language Processing

The smooth functioning of the language system requires integration between brain regions. Such integration was already noted in part by classical theorists who suggested that conduction aphasia results from a disconnection between posterior and anterior brain regions. Studies of comparative neuroanatomy indicate that the arcuate fasciculus that connects anterior and posterior language regions is not observed in other primates, hinting that this white-matter pathway may serve as an important basis for language processing in the human brain (Rilling et al., [2008](#)).

At present there is much controversy surrounding exactly how components of the language processing regions of the brain should be parsed into subsystems, and the particular circuitry of white-matter pathways that enables information from these different brain regions to coordinate their activity (e.g., Hickok and Poeppel, [2004](#), [2007](#); Grodzinsky and Friederici, [2006](#); Vigneau et al., [2006](#); Friederici and Gierhan, [2013](#); Fridriksson et al., [2016](#)). Nonetheless some broad generalizations are likely in order. As we have seen for other aspects of information processing, such as the processing of visual information, processing of language is also thought to rely on two separate streams of information: a dorsal stream, in this case conceptualized as more involved in phonological and motoric processing, and a ventral stream, in this case conceptualized as more involved in word-level (lexical) and semantic processing. The dorsal stream is thought to take linguistic information and transform it into articulatory information, whereas the ventral stream is thought to transform it to meaning.

As shown in [Figure 8.9](#), each of these two major pathways can be further subdivided. The first dorsal pathway links posterior regions of the superior temporal gyrus to premotor areas. This pathway allows auditory language information to be fed forward to premotor regions for articulation and language production. As this pathway allows the mapping of sound to motor output, it is thought to be especially important in repetition (Saur et al., [2008](#)). A second dorsal pathway connects superior temporal regions, mainly Wernicke's area, to Broca's area, via the arcuate fasciculus. This pathway likely allows for executive processes to be exerted on linguistic material, and aids in the processing of complex syntactic structure, such as when a sentence contains many clauses that must be integrated with one another (e.g., "At first surprised by the intensity of his own response, Matthew came to realize that his current reactions were most likely influenced by negative experiences during his childhood").

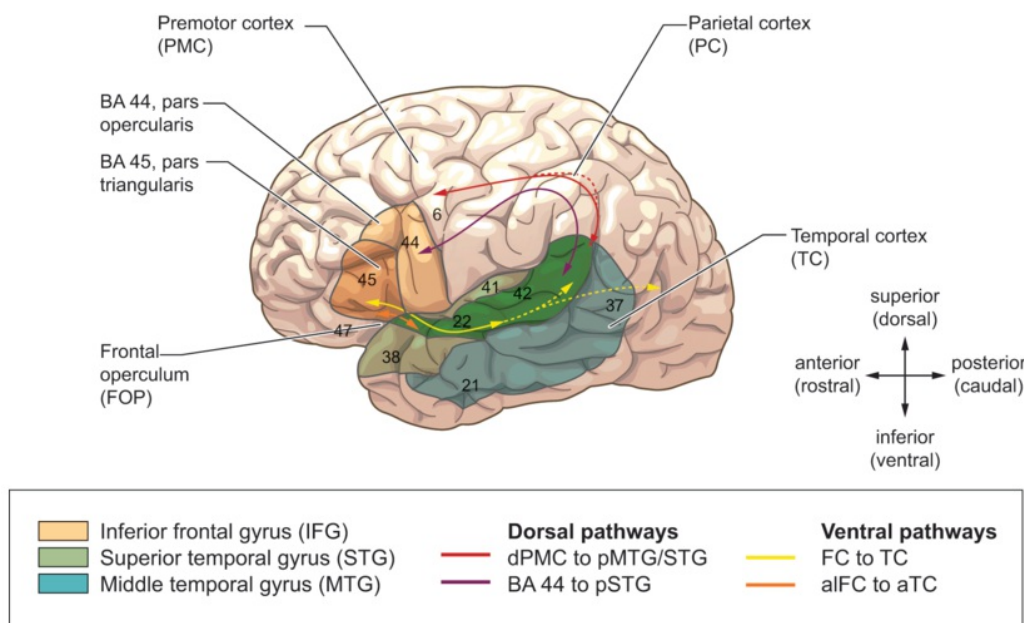


Figure 8.9 The four main pathways by which spoken language is processed.

Spoken language is processed initially in posterior portions of the left superior temporal lobe. Two dorsal pathways (shown in red and purple) are involved in phonological and motoric processing, while the two ventral pathways (shown in yellow and orange) are involved in word-level (lexical) and semantic processing.

(from Friederici and Gierhan, [2013](#))

The first ventral pathway connects posterior regions of the superior temporal lobe with more anterior temporal regions involved in semantics (we talk about this latter region in more detail in [Chapter 9](#) on memory). These regions are connected by the middle longitudinal fasciculus, which runs the length of the temporal lobe from posterior to anterior. This pathway is thought to be involved in linking phonology to semantics and meaning. These anterior temporal regions then connect with more anterior regions of the inferior prefrontal cortex that are involved in semantics, although the exact white-matter tract that supports such a connection remains unclear. Notice that while this first ventral pathway connects sound to meaning, the first dorsal pathway connects sound to action and articulation. Finally, the second ventral pathway, for which there is much less agreement, is thought to originate in anterior (rather than posterior) temporal regions and connect to ventral inferior frontal regions. It may support relatively simple syntactic processing that occurs on a more local level in sentence processing. For example, this pathway is thought to support the construction and comprehension of simple noun phrases consisting of a determiner, adjective, and noun, as in the phrase “the fluffy rabbit.”

One important idea about language that has come from this work on brain systems supporting language is that components of these systems can be used flexibly depending on the specific set of tasks or linguistic demands. Consistent with this idea the system that is preferentially utilized by a person may vary depending on experience, practice, or development. In one of the first studies to show such an effect, researchers examined the brain regions that are involved in generating a verb in response to a noun. When participants were naive to either the task or the particular set of stimuli used, activation occurred over the regions of the left hemisphere that when damaged typically cause Wernicke’s aphasia. However, when the participants were given a familiar and well-practiced set of stimuli, activation was more anterior, in an area typically associated with conduction aphasia (which, as you should remember, disrupts the ability to repeat sequences) (Raichle et al., [1994](#)).

From a developmental perspective, changes in the relative weighting of activity

across the different nodes of the language processing network occur as children become older and more fluent with language (e.g., Chou et al., [2006](#)). Still other research has shown that changes in the relative pattern of activity across regions can predict the learning of new phonemic contrasts (e.g., speech sounds in Hindi for non-Hindi speakers). Increased learning was correlated with greater activity in temporoparietal speech regions and less in frontal speech areas (Golestani and Zatorre, [2004](#)).

Thus far we have learned that in addition to lesion studies, various methods – such as electrical stimulation, Wada procedures, brain imaging, and electrophysiological studies – all provide evidence of left-hemisphere specialization for speech output, and for somewhat distinct neural systems for processing phonology, syntax, and semantics. Traditional models of language, based on patients who have suffered brain damage, suggest somewhat compartmentalized regions of brain tissue, each of which is involved in a specific aspect of language processing. However, newer neuroimaging and electrophysiological methods suggest a much more complicated and integrated language network spanning both anterior and posterior portions of the brain.

Visual “Spoken” Language

One important way to evaluate these models of the neurological bases of language is to examine “spoken” language systems that are not aurally based but are instead completely visual. American Sign Language (ASL), the language used by most deaf individuals in the United States, is one such language. In this manner, scientists can discern what is common across spoken language regardless of whether the information is conveyed in the auditory or in the visual modality. Not surprisingly, this work has focused on evaluating the more traditional models of language processing rather than the more recent conceptualizations. To preview, work on ASL suggests that brain organization for spoken language is similar, regardless of the modality of communication.

Basic Structure of American Sign Language (ASL)

To evaluate the evidence that ASL provides about the neural organization of language, we first need a brief introduction to the structure of this language. Each noun in ASL is represented by a particular hand shape that is made in a particular way at a particular location in space with regard to the body. Just as distinctive contrasts exist among phonemes (e.g., voicing), distinctive contrasts can be seen among signs in ASL. One distinctive feature that can be used to distinguish among different words is hand shape itself; another such feature is where that hand shape is made relative to the face. An example of three words in ASL that differ only in place of articulation is presented in [Figure 8.10](#).

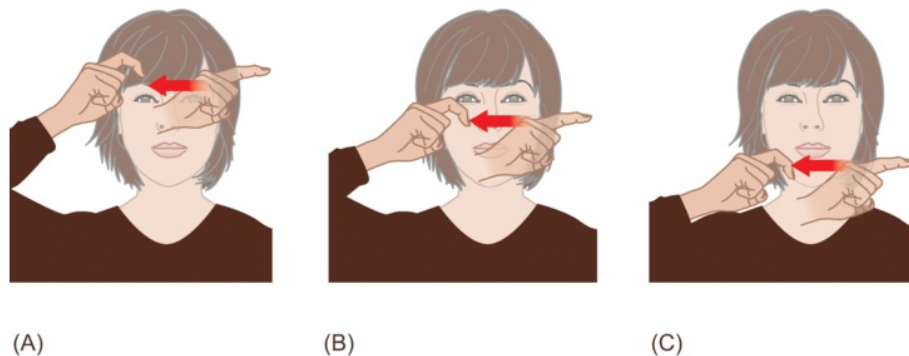


Figure 8.10 The distinctive contrast of place of articulation in American Sign Language.

The same hand shape has a different meaning depending on where the shape is produced. (A) If produced at forehead level, this sign means “summer.” (B) If produced at nose level, it means “ugly.” (C) If produced at the chin, it means “dry.”

Syntactic structure in ASL differs from that of spoken language. In ASL certain aspects of syntax are communicated through the position of the hands in space rather than through word order (e.g., SVO versus OVS) or by the type of hand movement rather than by word endings (e.g., -ly). When a sentence is produced in ASL, a noun is placed within a frame, or theater of space, that is directly in front of the speaker’s body. A speaker of ASL will make a hand shape for a noun and point to a particular location within this theater. Each noun in the sentence is given a different location in this theater.

A sign designating a verb (e.g., “bit”) is made from the location of the noun acting as the subject (e.g., “dog”) to the location of the noun acting as the object (e.g., “cat”). Thus, the syntactic distinction between subject and object is made spatially, by the direction of hand movement, as shown in [Figure 8.11](#).

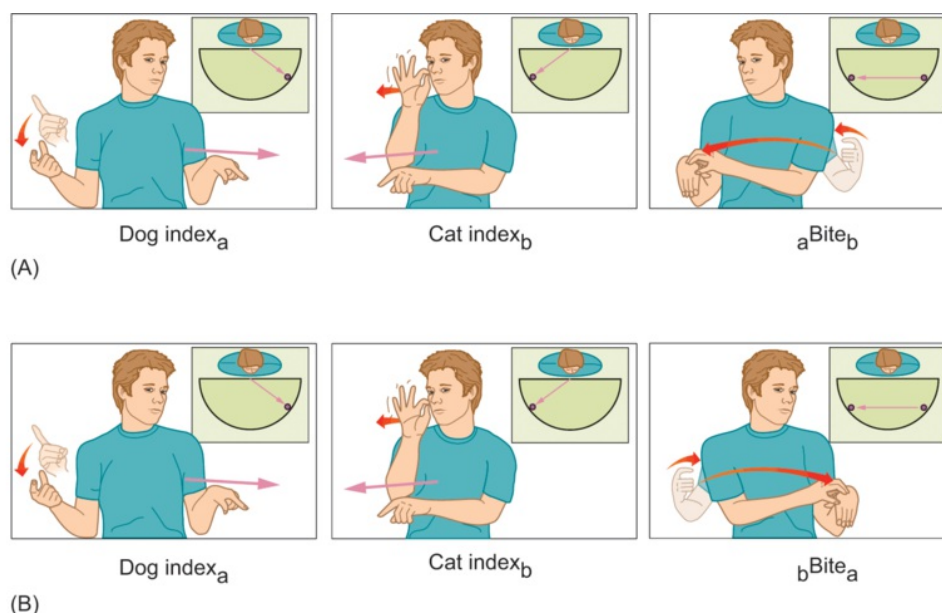


Figure 8.11 Spatial frame of reference in American Sign Language to make a syntactic distinction between subject and object.

(A) Here the individual is signing the sentence “The dog bit the cat.” First, the signer makes the sign for the word “dog” and notes a particular spatial location for this noun (left frame). Then he makes the sign for “cat” and notes a different spatial location to denote this noun (middle frame). He next makes the sign for “bit,” moving his hand from the “dog” position to the “cat” position (right frame). (B) In this case, the individual is signing the sentence “The cat bit the dog.” The procedure of signing this sentence is identical to that for the other sentence, except that the motion is made from the spatial position denoting “cat” to the one denoting “dog.”

The type of hand movement also provides syntactic information, such as inflections of a verb, which in English are indicated by different word endings (e.g., -ed, -ing). For example, if a person wants to say that something occurred repeatedly, the hand movement is different than if the event happened only once, just as in English an ongoing

action is indicated by an -ing ending. Examples of some of these distinctions are provided in [Figure 8.12](#).

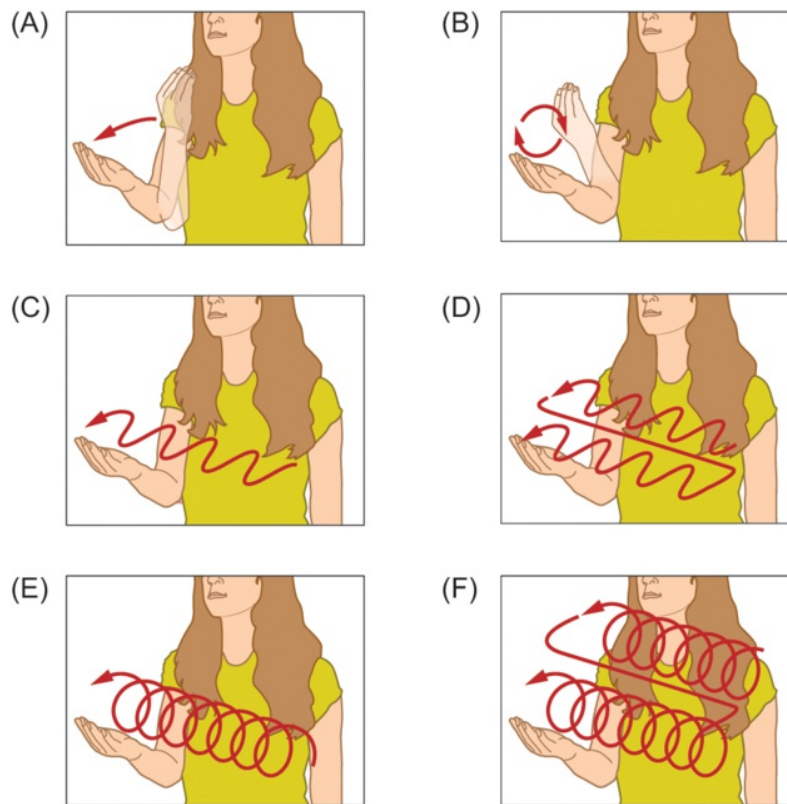


Figure 8.12 Examples of how variations in hand movement denote verb inflection in American Sign Language.

(A) The basic sign and hand movement for “give.” (B–F) Variations indicating the duration of the action and to whom it is directed. The various signs mean (B) “give continuously”; (C) “give to each”; (D) “give to each, that action recurring with time”; (E) “give continuously to each in turn”; and (F) “give continuously to each in turn, that action recurring with time.”

Neural Organization of ASL

Now that we know the basics about the structure of ASL, we can discuss the insights it provides into the brain’s neural organization for language (see Corina et al., [2012](#) for review). First, even though ASL is a visual language in which spatial processing plays a large role in syntax, it appears to be dependent on the left hemisphere. The

comprehension of signs is more disrupted by damage to the left hemisphere, especially left temporal regions, than by damage to the right hemisphere (Hickok et al., [2002](#)).

Second, case studies of native speakers of ASL who have become aphasic reveal that, as in spoken language, there is a distinction between anterior and posterior language systems (Poizner et al., [1987](#)). As seen with standard English, damage to either of these two systems has different effects on comprehension versus production, and syntax versus semantics. Those with anterior damage exhibit a paucity of signs and a lack of fluency. Their production of ASL is agrammatic, with disruptions of hand movements that serve as syntactic markers and loss of the elaboration of hand movements that act as inflections. In contrast to these difficulties, the signs produced are semantically correct. Following is an example of one native speaker of ASL, who sustained a large lesion to her left frontal lobe, attempting to relate a story from her childhood. Notice that she had little difficulty comprehending the examiner's questions.

EXAMINER: What else happened?

GAIL D.: car ... drive ... brother ... drive ... I ... S-T-A-D [attempts to gesture "stand up"]

EXAMINER: You stood up?

GAIL D.: Yes ... I ... drive ... [attempts to gesture "wave good-bye"]

EXAMINER: Wave goodbye?

GAIL D.: Yes ... brother ... drive ... dunno ... [attempts to gesture "wave good-bye"]

EXAMINER: Your brother was driving?

GAIL D.: yes ... back ... drive ... brother ... man ... mama ... stay ... brother ... drive.

(Poizner et al., [1987](#), p. 120)

Converging evidence for the role of Broca's area in speech production in ASL is provided by a case study of a deaf signer who produced errors in sign production when Broca's area was cortically stimulated (Corina et al., [1999](#)).

Another signer whose damage included anterior regions but also extended to posterior regions exhibited a linguistic profile that was more like that of a person with Wernicke's aphasia. His signing in ASL, as well as his writing, was fluent but did not have much meaning. The following is a translation of a sample of his signing in which he described the layout of his apartment, which had a glass-enclosed patio off the living room:

And there's one (way down at the end) [unintelligible]. The man walked over to see the (disconnected), an extension of the (earth) room. It's there for the man (can live) a roof and light with shades to (keep pulling down). And there's a glass wall with four different He hammered. The man (makes hands), makes mobiles, many on the wall. A wonderful (always brillianting) man.

(Poizner et al., [1987](#), p. 98)

Evidence from ERPs also suggests a distinction between semantic and syntactic processing in ASL. When native deaf speakers are presented with signed sentences containing a syntactic error, a late positivity (i.e., P600) is observed. When presented with sentences containing a semantic error, an N400 is elicited, similar to that observed for spoken languages (Capek et al., [2009](#)).

Third, numerous neuroimaging studies demonstrate that organization of regions within the left hemisphere for language processing is highly similar for ASL and spoken language. For example, the same set of regions of the left hemisphere are activated in tasks such as the naming of single words in ASL or the production of narratives in ASL as is observed when these tasks are performed for spoken language (see MacSweeney et al., [2008](#) for review).

Nevertheless, not everything about the neural underpinnings of spoken language and sign language is identical. For example, when asked to name concrete objects, signers activate two regions of the left parietal lobe to a greater degree than hearing speakers. One of these is located in the supramarginal gyrus and may reflect phonological aspects of processing in ASL, such as the selection of distinctive features (e.g., hand configuration, place of articulation). The other is within the left superior parietal lobe and may reflect proprioceptive monitoring of the motoric output that is being produced (Emmorey, Mehta, and Grabowski, [2007](#)). Moreover, there tends to be greater right-hemisphere activation in signers than in hearing individuals who utilize a spoken language. Because individuals who sign are usually deaf, it is impossible to know whether this activation results from deafness or from use of a sign language. To disentangle these two possibilities, researchers compared patterns of brain activation in deaf individuals who are native signers of ASL with patterns in hearing individuals who are bilingual from birth in spoken English and ASL (these individuals are typically born to deaf parents). This investigation found that native speakers, both hearing and deaf, not only activate classic language areas of the left hemisphere when processing language materials, but also activate homologous regions of the right hemisphere (Neville et al., [1998](#)). One might think that this activation merely reflects the fact that this language is visual and spatial. However, activation of some regions of the right hemisphere, such as the angular gyrus, occurs only in native speakers, not in those who learn sign language after puberty (Newman et al., [2002](#)). Accordingly, the activation in native speakers appears to indicate a recruitment of right-hemisphere regions for language processing. Supporting this idea are findings of changes in brain morphology – specifically, increased white matter in the insula of the right hemisphere – in both deaf and hearing native speakers of ASL compared to individuals with no knowledge of ASL. This white matter may allow increased cross-modal sensory integration in signers (Allen et al., [2008](#)).

In addition, one can examine the pattern of activation across different sign languages. Just as English and Chinese are distinct languages, so are different sign

languages. Knowing ASL will not help a person understand Chinese Sign Language. To look at the commonalities across sign languages, researchers have compared patterns of brain activation in speakers of ASL to patterns in speakers of Langue des Signes Québécoise (LSQ), which is a sign language used in Quebec and other parts of French Canada (Petito et al., [2000](#)). They found that the pattern of activation does not vary significantly depending on the type of sign language used. More surprisingly, regions within the superior temporal gyrus that were thought to be dedicated to processing information in the auditory modality produced activation when deaf individuals processed sign nonwords! These results suggest that these regions are not specialized for auditory processing per se, but are dedicated to processing basic units of a complex pattern in rapid temporal sequence, an ability that could underlie either an auditory or a visual language (see [Figure 8.13](#)).

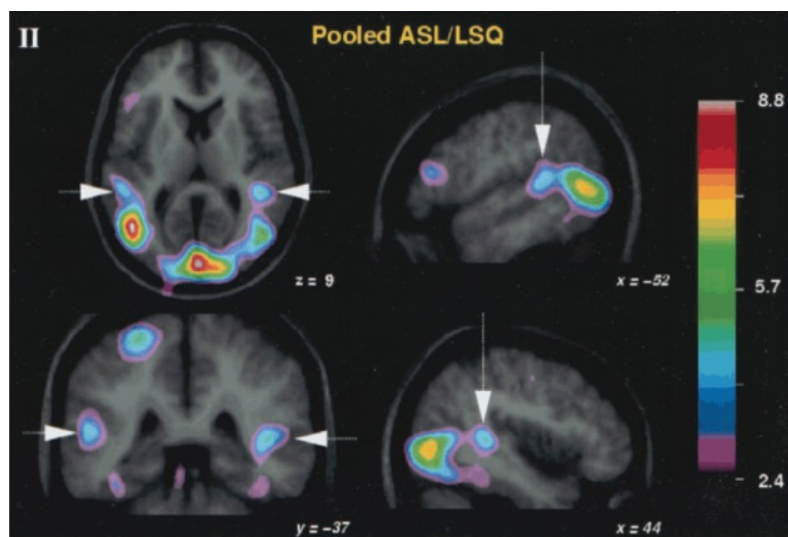


Figure 8.13 Activation of “auditory areas” in deaf individuals.

Shown by the arrows is activation in the superior temporal gyrus of speakers of American Sign Language (ASL) or the Sign Language of Quebec (SLQ) while they are reading words or legal nonwords in sign. Red shows the highest area of activity.

(from Petito et al., [2000](#))

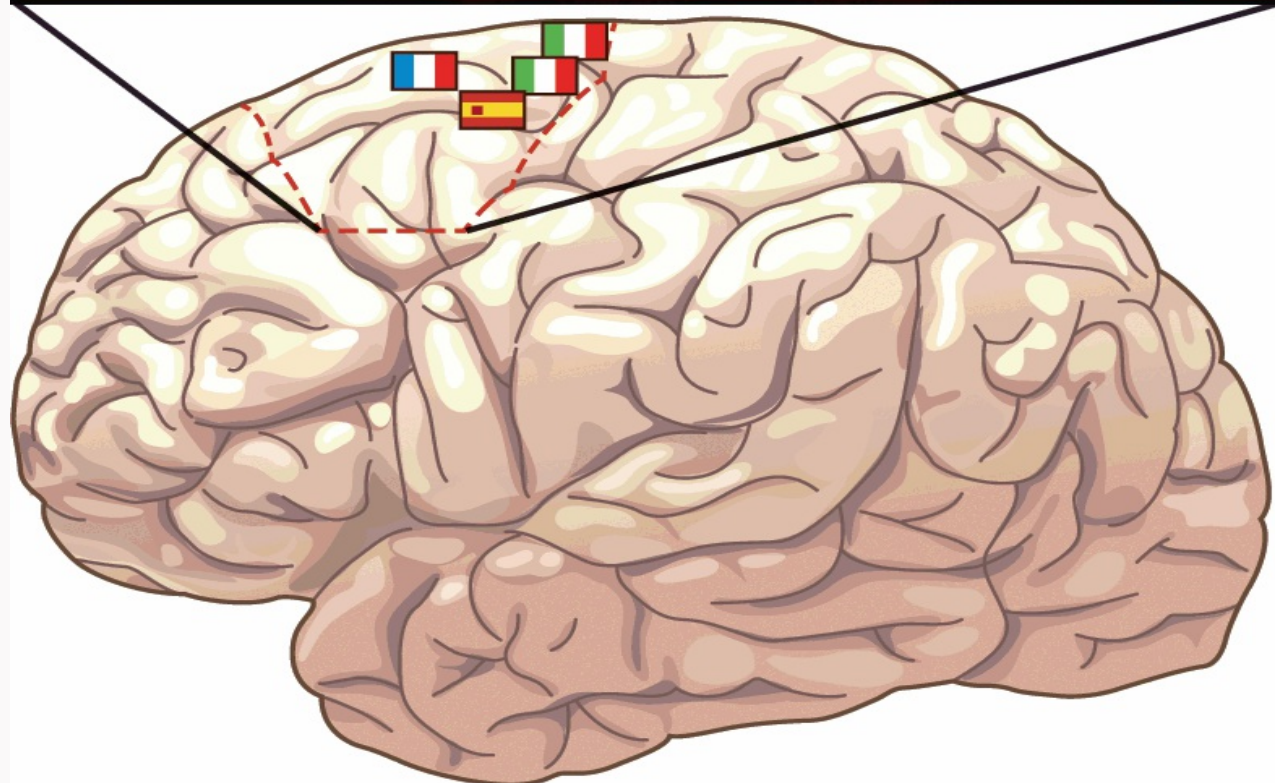
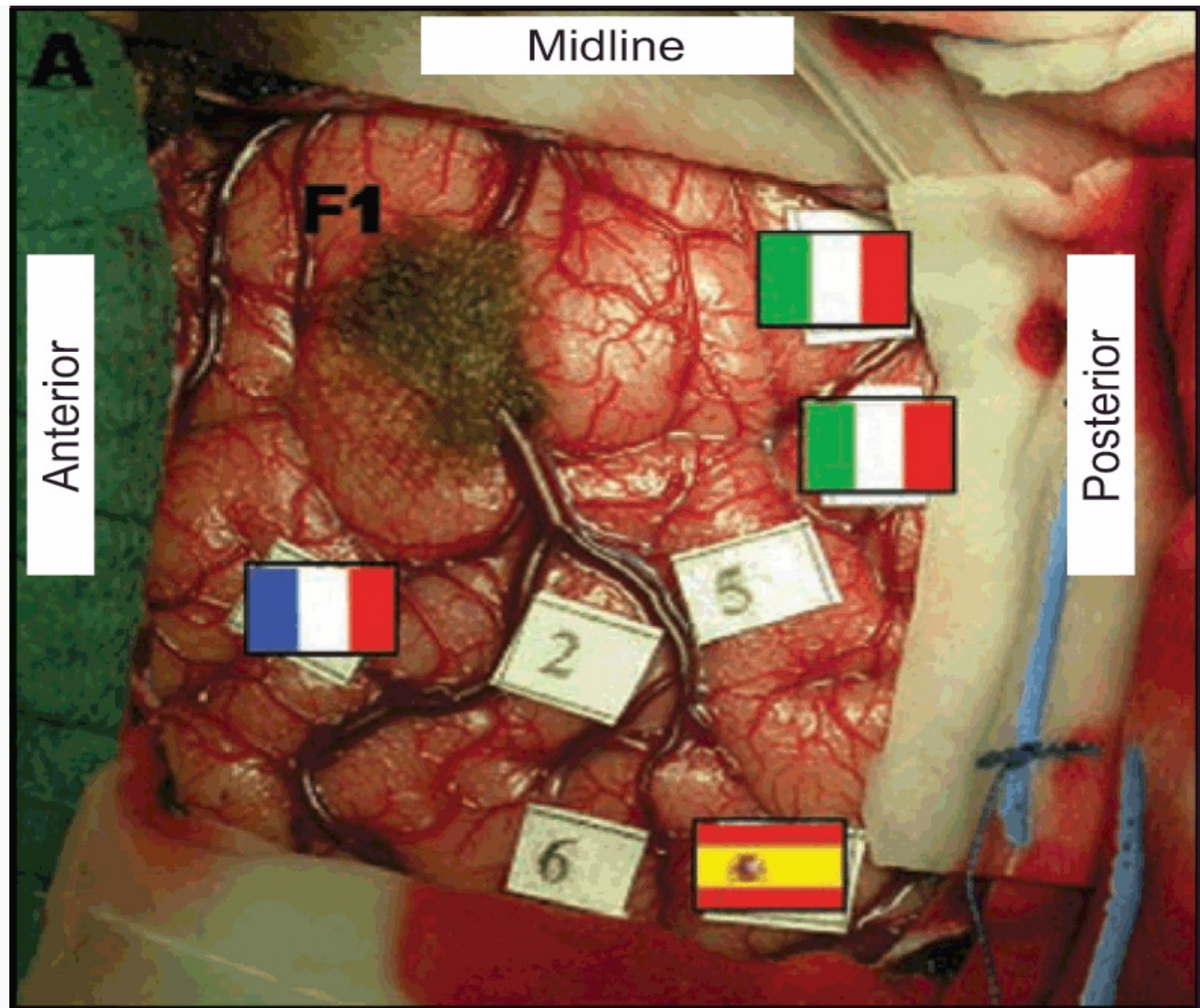
In sum, the evidence from speakers of sign language indicates that the left hemisphere plays a large role in language processing, regardless of the modality

(speech, vision) in which that language is expressed. Moreover, the subcomponents of the network of regions involved in language processing are similar across spoken and signed languages. However, processing of sign language appears to recruit right-hemisphere regions to a greater degree than spoken language.

In Focus: Brain Organization in Bilinguals

Understanding the psychological and neural mechanisms of a single language may seem like a nearly insurmountable task, but now consider that most of the world's population is fluent in more than one language. The phenomenon of bilingualism raises intriguing questions about language. How are two languages organized within the same brain? Do they rely upon separate or different neural systems? How does the brain shift between two or more language systems?

Traditionally, cognitive neuroscientists have tried to understand the bilingual brain by examining the pattern of disability following brain damage from stroke or from cortical stimulation studies. While in most cases, aphasia in bilinguals follows left-hemisphere damage, just like aphasia in mono-linguals, there is an extremely wide variation in the pattern of deficits and recovery (Lorenzen and Murray, [2008](#)). Some patients show aphasia in both languages, some show deficits in the native language but not a second language, and yet others show more severe deficits in the second language. A similarly complicated picture is derived from studies of cortical stimulation of bilingual patients undergoing neurosurgery, with disagreement across studies as to the location and extent of brain areas specific to second-language processing (e.g., Lucas et al., [2004](#); Giussani et al., [2007](#)) (see [Box Figure 8.1](#)).



BOX Figure 8.1 Cortical stimulation evidence for the dissociation of language processing in bilinguals.

Shown here are areas that elicited a language-specific response in a native speaker of Italian who learned French and Spanish as an adult and used those languages daily at work. The region for each language is depicted by the flag of that country (red, white, green – Italy; red, white, blue – France; yellow, red, black – Spain).

(from Giussani et al., [2007](#))

Several variables complicate the seemingly simple question of understanding whether two languages rely upon the same brain system in bilinguals. First, bilingual people differ in the age at which they acquired their first and second languages (often referred to as L1 and L2, respectively). Some people are exposed to two languages from birth, often referred to as simultaneous bilinguals, whereas others learn L1 from birth but acquire L2 at a later age, often referred to as sequential bilinguals. In addition, bilingual people differ in their level of proficiency in L2; some reach a level of fluency that equals their fluency in their native tongue, whereas others are considerably less fluent in L2 than in L1. Finally, we need to consider which aspect of language is being examined. Whether two languages share common neural substrates may depend on whether we are examining brain regions involved, for example, in syntax as compared to semantics. As we will see, despite these complicating variables at least some general conclusions can be drawn.

Brain imaging studies have attempted to address this basic question (whether two languages depend on the same brain systems), while taking into account some of the variables just discussed. One approach is to compare the pattern of brain activation in mono-linguals to people who acquired that same language later in life (i.e., second-language learners). In general, brain activations for mono-linguals and second-language learners seem to overlap to a large degree in

most studies, and this degree of overlap is higher when L2 is acquired early rather than late. In other words, there is no evidence that radically different brain regions are used for L2 than for L1.

However, in general, second-language learners, compared to native speakers, tend to show increased activation in some language-related regions, as well as in regions involved in executive processes. This pattern has been demonstrated for a variety of language processing tasks including reading sentences with complex syntax (e.g., Weber et al., [2016](#)) and comprehending them even when performance levels are similar across the groups (Román et al., [2015](#)). Such a pattern suggests that speaking a second language is more effortful and less automatic and that mono-linguals process linguistic information more efficiently (Palomar-Gar'cia et al., [2015](#)). There is also some suggestive evidence that since second languages may require greater integrity or activation of the language system, they are more susceptible to disruption following brain damage (Hope et al., [2015](#)).

Another way to examine this issue is to compare patterns of language activation within the same individuals for L2 versus L1 (rather than across individuals as just discussed). A recent meta-analysis supports the idea that similar brain regions are activated for both languages, but that additional regions may be activated for L2 (Liu and Cao, [2016](#)). This finding also suggests that processing a second language is more demanding, in this case, requiring additional “neural machinery” as compared to a first language.

These effects, not surprisingly, are influenced by the age of acquisition of the second language (Sakai et al., [2009](#)). Meta-analyses suggest that fewer additional regions are recruited for L2 in simultaneous bilinguals than sequential bilinguals (Liu and Cao, [2016](#)). One study found that in simultaneous bilinguals there was very little difference in the brain regions engaged while reading aloud. For sequential bilinguals, however, the later the age of acquisition, the larger was the degree to which additional brain areas, including premotor, left inferior

frontal, and fusiform cortex, were recruited for reading in the second language (L2) (Berken et al., [2015](#)).

Learning a second language not only affects what areas of the brain activate during language tasks, but may also influence the actual anatomy of the brain (see Li et al., [2014](#) for review). There is some evidence that structural changes are observed in brain areas that need to be recruited more during language tasks in individuals who learned a second language later in life. For example, alterations in gray-matter characteristics are observed in the left inferior frontal cortex in late learners of a second language as compared to those who learned both languages earlier in life (Klein et al., [2014](#)) and in the left inferior parietal cortex of bilinguals compared to mono-linguals (Mechelli et al., [2004](#)). Effects are not limited to gray matter, however, as increased integrity of white matter between language-related brain regions is found in older individuals who have been bilingual their whole lives (i.e., simultaneous bilinguals) (Luk et al., [2011](#)) as well as for those who acquired their second language earlier in life, during the school-age years (i.e., sequential bilinguals) (Pliatsikas et al., [2015](#)). These effects are influenced in complicated ways both by age of acquisition of a second language as well as the degree of proficiency and immersion in the second language (Nichols and Joanisse, [2016](#); Pliatsikas et al., [2017](#)). Researchers are continuing to work to gain a better understanding of the influence of age of acquisition and proficiency on brain organization for a second language.

While these studies suggest that learning a language influences brain organization, the opposite may also be true. An individual's intrinsic brain organization may influence how easy or hard it may be for that person to learn a second language. (This is a comforting thought to at least one of the authors of this textbook, whose difficulty in meeting a foreign language requirement almost derailed her ability to receive a PhD!). For example, increased gray-matter volume and white-matter connectivity of Heschl's gyrus is associated with better

learning of novel speech sounds (e.g., Golestani et al., [2007](#)) and more highly correlated activity at rest between anterior and posterior brain regions involved in language predicted better ability to retrieve and say words in a second language (Chai et al., [2016](#)). Thus an individual's brain anatomy may influence how well he or she can acquire new language skills. (For a longer discussion of how aspects of brain morphology are associated with language skill, see Richardson and Price, [2009](#).)

A final issue involves how the bilingual brain manages to coordinate processing across two language systems. Some bilinguals may engage in “code-switching” several times within a single conversation, mixing words from the two languages, and others may switch between languages only when in different situations, such as at school versus at home. In both cases, though, the brain must be able to select a particular language and then overcome conflicts arising from the other language (e.g., Abutalebi et al., [2007](#)). Such conflict seems to be inevitable, as fMRI (van Heuven et al., [2008](#)) and ERP studies (Martin et al., [2009](#)) indicate that when a word is read in one language it also becomes available in the other, suggesting simultaneous activation of both language systems. Evidence suggests that brain regions involved in executive control (discussed in more detail in [Chapter 11](#)) are involved in the code-switching required to manage two languages within one brain (van Heuven et al., [2008](#)). In fact, acquiring two languages may actually have the unanticipated side effect of increasing executive abilities (see Kroll and Bialystok, [2013](#), although see Morton, [2010](#), for critique of the evidence). Indeed, there may be many good reasons to learn another language besides the opportunity to explore other cultures and travel abroad comfortably!

Neurological Bases for Visual Language Processing

As we discuss in this section of the chapter, the neural machinery for spoken and written language is somewhat distinct. If you think about it, this fact should not be especially surprising. First, these two types of language processing occur in different modalities (auditory versus visual). To the degree that they interact with different sensory regions of the brain, they might be presumed to differ in their neural organization. Second, although spoken language has existed for some time in human evolution, written language is a relatively new invention. The organization of the brain is likely to have undergone evolutionary pressure for the development of spoken language; not enough time has passed for that to be the case for written language. Third, as we see in the following section, interpretation of written language does not always rely on using spoken language as an intermediary. To the degree that processing of visual words is independent of spoken language, these two types of language processing might be expected to have different neurological bases.

Evidence From Studies of Patients With Brain Damage

As we observed when discussing the neurological bases for auditory language processing, studies of patients with brain damage also suggest dissociations between different language subsystems. In particular, while one may consider reading and writing to be two sides of the same coin, there are ways in which they are distinct.

Alexia Versus Agraphia

Just as the production of spoken language is distinct from the perception of spoken language, so too is the production of written language (writing) distinct from the perception of written words (reading). When the ability to read is lost as a consequence of brain damage, the ensuing syndrome is known as [alexia](#) or acquired dyslexia (to distinguish it from developmental dyslexia, in which a person has great difficulty acquiring the ability to read during childhood; see [Chapter 15](#)). When instead the ability to write is lost, the deficit is known as [agraphia](#).

Although alexia and agraphia typically co-occur after damage to the angular gyrus (located in the ventral region of the parietal lobe above the Sylvian fissure), the two can dissociate. In some cases individuals have alexia without agraphia (e.g., Greenblatt, [1973](#)), and in other cases agraphia without alexia (e.g., Hécaen and Kremin, [1976](#)). These dissociations can lead to some strange situations. Although a person who has alexia without agraphia can write a sentence with little difficulty, that person is unable to read sentences, including those that she or he previously wrote! Likewise, people who have agraphia without alexia are unable to write sentences, but can read without much difficulty. As you should recognize by now, the syndromes of alexia without agraphia and agraphia without alexia are examples of a double dissociation. In this case, the double dissociation indicates that the neural control systems for reading and writing are separable to some extent and do not critically rely on each other.

Reading

To better understand how the brain processes written language, we first examine the cognitive processes underlying written language. Here we use reading as an example, then later describe how these findings generalize to writing.

Phonological Versus Direct Route to Meaning

Researchers have proposed two distinct routes whereby information in a visual linguistic format can be linked to meaning (e.g., Coltheart et al., [2001](#)). The first route is known as the phonological (or nonlexical) route to reading because sound is a mediator in the process of associating print with meaning. This route, which you likely used when learning to read, requires you to identify each letter (e.g., c, a, t), sound out each letter (/k/, /a/, /t/), and then blend the three sounds to produce a word (“cat”). Once you pronounce the word, you can recognize its meaning because you already associate this sound pattern with the concept that it represents (“a small, furry household pet with claws that is known for its taste for tuna and mice and for an aloof

and independent demeanor"). Thus, the auditory sounds were the intermediary allowing you to link print to meaning.

The rules whereby print is associated with sound are known as grapheme-to-phoneme correspondence rules. Graphemes are the smallest units of written language that are combined to make words. For example, the visual pattern "c" is a grapheme, and this grapheme can take many forms, such as "c," "c," "C," and "C." Grapheme-to-phoneme correspondence rules let us know how each grapheme should sound (e.g., "c" is usually pronounced /ka/) and how graphemes should be combined. For example, these rules dictate that for most words ending in vowel-consonant-"e" (e.g., lake, mike), the first vowel is long and the final "e" is silent.

The second route is known as the direct (or lexical) route to reading because print is directly associated with meaning, without the use of a phonological intermediary. For a certain proportion of words in the English language, the direct route must be used because these words, known as irregular words, do not follow grapheme-to-phoneme correspondence rules and so are impossible to sound out correctly. If grapheme-to-phoneme correspondence rules are used to pronounce colonel, for instance, the result will be the incorrect "koe-loe-nell," rather than "kur-nel." When the direct route is used, an association is made between a particular visual form of a word (e.g., colonel) and its meaning (e.g., "a high-ranking military officer whose rank is just below that of a general").

Neuropsychological Evidence for These Two Routes

Evidence from patients with brain damage has suggested that these two routes can be used independent of each other. To assess the integrity of the phonological route, researchers examine how well individuals can read words they have never seen before. For such new words, no prior linkages from the visual form to meaning would exist, making direct access impossible. Reading nonwords requires the phonological route because nonwords have no meaning. (For instance, until now, you probably never saw the nonword glimay, but you can read it using your knowledge of grapheme-to-phoneme

correspondence rules.) Likewise, investigators assess the integrity of the direct route by determining how well people can read words that do not follow the grapheme-to-phoneme correspondence rules (i.e., common irregular words), such as colonel and yacht.

One set of patients, who have a syndrome known as [surface dyslexia](#) (or surface alexia), have a disruption in the direct route but not in the phonological route. Their syndrome is so named because these individuals cannot link the surface information – that is, the visual form of a word – directly to meaning. Such individuals cannot read irregular words correctly, but rather sound them out (using the phonological route) and hence misread them. They often confuse homophones, which are words that sound the same but have different meanings, such as beat and beet. Thus, when asked to define the word pane, these patients may say “to feel distress,” or when asked to define mown, they may say “to complain.” Their spelling errors also indicate their reliance on the phonological route because their spellings are often phonologically correct but graphemically incorrect (e.g., writing whisk as wisque, or mayonnaise as mayenaze) (e.g., Coltheart, [1982](#); Shallice et al., [1983](#)). In contrast, they have no difficulty reading nonwords or regular words, because their phonological route is intact.

People with the contrasting syndrome, [phonological dyslexia](#) (or alexia), have a disrupted phonological route but an intact direct route. They have relatively little trouble reading previously learned words, because meaning can be extracted directly from the visual form regardless of whether the words are regular or irregular. Their disability becomes apparent only when they are asked to read nonwords or words with which they are unfamiliar. In these cases, the direct route does not suffice, because the person does not have an association between the visual form and meaning (e.g., Patterson, [1982](#)). Without that association, the person must rely upon sounding out words through the phonological route, which is disrupted in phonological dyslexia.

There is a syndrome related to phonological alexia known as [deep dyslexia](#) (or alexia). People with this disorder show many of the deficits exhibited by those with

phonological alexia (such as the inability to read nonwords), but they also show additional difficulties. First, when reading, they often make [semantic paralexias](#), which are reading errors in which a word is misread as a word with a related meaning. For example, forest may be read as “woods” and tulip as “crocus.” Second, these people have more difficulty reading abstract words (e.g., sympathy, faith) than words that represent concrete entities in the physical world (e.g., refrigerator, basket). Third, these patients have difficulty reading small function words that serve as grammatical markers.

Because of this constellation of symptoms and its similarity to the reading capabilities of the isolated right hemisphere of split-brain patients (Zaidel, [1990](#)), the syndrome of deep dyslexia may represent reliance on the right hemisphere for reading (Coltheart, [2000](#)). Supporting this claim, one study found that a patient with a developmental variant of the disorder exhibited right-hemisphere activation during reading (Pitchford et al., [2007](#)). But other researchers have argued that this behavioral pattern merely reflects the remaining ability of the left hemisphere to process language after multiple regions within it have been damaged (Morton and Patterson, [1980](#)), rather than a shift to right-hemisphere processing of language. Currently, anatomical patterns of damage as observed in patients do not definitely distinguish between these two possibilities (Ripamonti et al., [2014](#)).

Nonetheless, the dissociations in patterns of deficits across disorders speak to the fact that written language can either rely on phonology to access meaning or bypass phonology. Nevertheless, in everyday life both routes are probably used. In fact, researchers can predict overall reading ability by assessing the ability to read irregular words (tapping the direct route) and nonwords (tapping the phonological route), both in young normal readers, in children with reading impairment (Coltheart et al., [2001](#)), and in individuals with acquired alexia (Rapcsak et al., [2007](#)).

Writing

Just as there are two routes to reading, studies of patients with unilateral brain damage suggest that two routes can transform thoughts into writing. One route goes from thought

directly to writing, whereas the other uses phoneme-to-grapheme correspondence rules as an intermediary. In **phonological agraphia**, individuals can manually or orally spell regular and irregular words in dictation but perform poorly with nonwords (e.g., Shallice, 1981). In **lexical agraphia**, the opposite occurs: a reasonable spelling can be produced, both manually and orally, for virtually any regular word or nonword, but spelling of irregular words is poor (e.g., Beauvois and Derouesne, 1981). Just as with reading, writing seems to entail two routes, a direct one and a phonological one. Although you may have anticipated such a distinction on the basis of what we learned about reading, this need not have been the case. Even though reading and writing are similar, the process of writing is not just reading in reverse order. For example, phoneme-to-grapheme rules are not the opposite of grapheme-to-phoneme rules. Consider the following case in point. Although /k/ is the most common sound for the grapheme “k,” the most common grapheme for the sound /k/ is “c.” Nevertheless, in both reading and writing, there appear to be both phonological and direct routes that associate the written form with meaning.

Converging Evidence From Other Research Methods

Just as we saw with spoken language, studies of people with brain damage provided fundamental insights into the neural systems supporting written language. But also like spoken language, the advent of neuroimaging and other techniques that are used with neurologically intact people have moved us beyond conceptualizations of specific brain regions performing specific compartmentalized functions. In this section, we discuss what these methods can tell us about how the brain performs both the precentral (i.e., prior to meaning) and central (i.e., linking form to meaning) aspects of reading. We start by discussing how brain imaging studies, electrophysiologic studies, and behavioral studies of neurologically intact people provide insights into how the brain processes visual word forms.

Initial encoding of word forms is handled in different ways by the left and right hemispheres. The right-hemisphere system encodes words in their specific visual form,

whereas the left-hemisphere system extracts an abstract representation of word form that is common across different instances of a word, such as variations in font or case. Evidence supporting this difference comes from priming studies of neurologically intact subjects. If a particular physical shape of a word (e.g., uppercase) is presented to the right hemisphere, subsequent processing of that word is facilitated to a greater degree when it appears in the same case (i.e., uppercase) than when it appears in a different case (i.e., lowercase). However, priming is equivalent in the left hemisphere regardless of the case of the prime (e.g., Burgund and Marsolek, [1997](#); Marsolek and Deason, [2007](#)). This hemispheric difference is probably not specific to words, but represents hemispheric asymmetries in how visual information is processed in general.

The earliest stage of word processing that appears to be lateralized to the left hemisphere consists of mechanisms that are sensitive to the rules that govern how letters are combined, known as orthography. This process occurs rapidly at around 200 milliseconds post-presentation, with ERPs in response to words converging regardless of whether a word is presented in the RVF or the LVF, suggesting a common processing mechanism in the left hemisphere (Cohen et al., [2000](#)). MEG recordings detect a similar process at about 150 milliseconds post-presentation. These MEG studies (Tarkiainen et al., [1999](#)) along with fMRI studies indicate that such activity occurs in inferior occipital-temporal regions of the left hemisphere, bordering the fusiform gyrus (Brodmann area 37). This area has been dubbed the visual word form area, because it seems to activate regardless of the word's spatial position and is more active during tasks that require orthography (e.g., read words) compared to those that do not (e.g., consonant strings) (Petersen et al., [1990](#); Cohen et al., [2000](#)) (see [Figure 8.14](#)).

Definition of ROIs

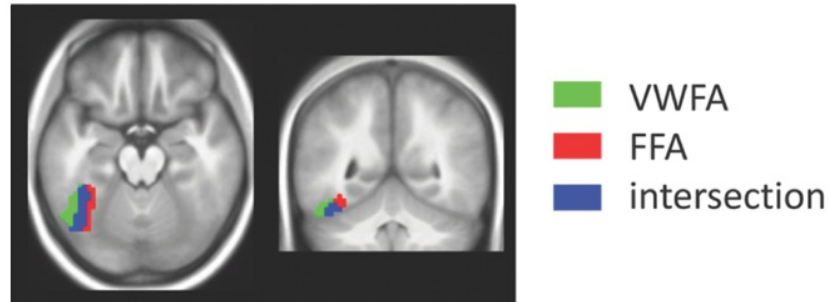


Figure 8.14 The location of the visual word form area (VWFA).

This area is thought to be responsible for identifying the invariant nature of written words regardless of their size, font, or position. Notice that its location is in the ventral visual processing stream. While it overlaps somewhat with the fusiform face area, it is located more laterally.

Although the visual word form area has been suggested to represent abstract orthography, Kronbichler et al. (2009) found that it showed greater activation to case-deviant and letter-deviant forms compared to familiar forms of the word (e.g., “TaXi” and “Taksi” versus “Taxi”). This finding is consistent with some speculations that activity in this region may not be specific to orthography. Rather, like other regions of the fusiform gyrus that show increased activation in individuals with specific expertise in classifying particular types of objects such as birds and cars (see Chapter 6), this region may become tuned to the recurring properties of a writing system of words (McCandliss et al., 2003; Wandell, 2011). As such, it is important for reading because it allows the legal and common combinations of letters within a language to be easily identified.

Brain imaging studies have attempted to provide more information about the areas involved in the direct and phonological routes than can be gleaned from the relatively rare case studies of phonological or surface alexia. (Some neuroimaging studies of word reading have also been performed on these rare patients; see Price et al., 2003.) To investigate the phonological route, researchers examine which brain regions are more active when the person has to read pseudowords, which critically rely on a

translation of orthography to phonology, as compared to regular or irregular words. Alternatively, researchers may compare activity for word naming to picture naming, because naming either a picture or a word requires a linkage of phonology and semantics, but only in word naming will there also be a translation of orthography to phonology. To investigate the direct route, researchers examine which brain regions are more active when one has to read irregular words compared to regular words, because irregular words can only be recognized via the direct route. Alternatively, researchers attempt to find regions that are more active in response to real words, which can utilize a direct semantic route, compared to nonwords, which cannot.

Studies suggest that some brain regions are more involved in the phonological route than the direct route, and vice versa (Jobard et al., [2003](#); Graves et al., [2010](#)). Phonological analysis of words appears to rely on a more dorsal route and activates three major regions. First is the superior and middle temporal gyrus, which is likely to be involved in accessing sounds related to letters. Second is supramarginal gyrus, in the inferior parietal lobe, which is likely to play a major role in symbol-to-sound transformation as is required in grapheme-to-phoneme conversions. Third is activity in Broca's area (BA 44), which is likely to play a role in linking phonology to speech.

In contrast, the direct route appears to activate a ventral route and somewhat different regions. The first area is in the most posterior section of the superior temporal sulcus up into the angular gyrus. The second is a middle and ventral region of the inferior temporal gyrus, which may sustain semantic processing of words and objects. Finally, it activates anterior regions of the inferior frontal gyrus (area 45), which as we discussed earlier is also involved in semantic processing (see [Figure 8.15](#)).

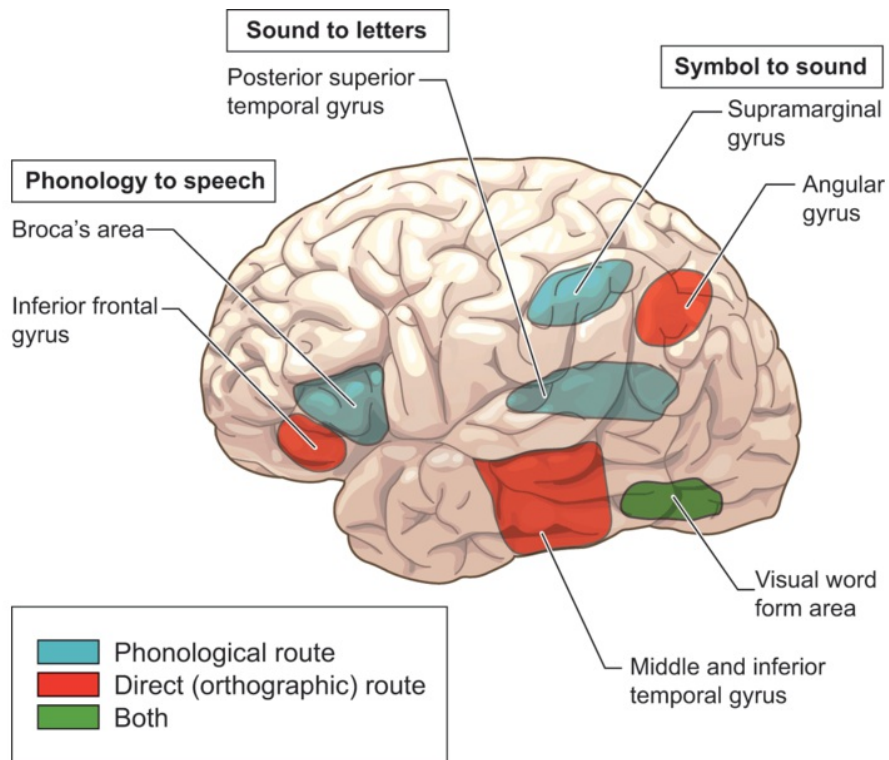


Figure 8.15 The brain regions involved in the direct and indirect routes to meaning.

The regions involved in the indirect route, in which phonology is linked to meaning are shown in blue. The regions involved in the direct route, in which print is translated directly to meaning, bypassing phonology are shown in red.

Because there are two potential routes, the way that reading is accomplished can vary depending on the task demands and the nature of the language. For example, during the reading of pseudowords (which would be more likely to require the phonological route), activity in the angular gyrus is most highly correlated with activity in other areas that are involved in phonological processing, such as superior temporal regions (BA 22) and Broca's area. In contrast, during the reading of real words, activity in the angular gyrus is more highly correlated with activity in regions in occipital and ventral temporal cortex, which are more often associated with the direct route (Rumsey et al., [1997](#)).

Similarly, statistical models of connectivity between brain regions suggest that input from posterior temporal regions to posterior frontal regions is greater during the reading

of pseudowords than regular or irregular words, whereas input from anterior temporal regions to anterior frontal regions is greater during the reading of irregular words than pseudowords or regular words (Mechelli et al., [2005](#)). These findings suggest that it may be the relative level of activity across each of a set of language-related brain regions, as well as their relative connectivity with other portions of the language network, that distinguishes the direct route from the phonological route to reading.

The relative reliance on each route may also depend on the nature of the language. For example, orthography in Italian is referred to as consistent (sometimes also referred to as shallow) because there are reliable rules for the conversion of graphemes to phonemes that yield correct pronunciation of the word. Orthography in English, in contrast, is much less consistent (sometimes referred to as deep). A famous example of this is the comment by George Bernard Shaw that “ghoti” could be read as “fish,” if the “gh” were pronounced as in “enough,” the “o” as in “women” and the “ti” as in “nation.” When reading real words, Italian people showed more activation in left superior temporal regions than English readers, consistent with a reliance on phonological processing when decoding written language. In contrast, when reading nonwords, English readers exhibited more activation in left inferior posterior temporal regions and anterior portions of the left inferior frontal gyrus compared to Italians (Paulesu et al., [2000](#)). Because these regions of the brain are typically associated with the direct route, these results suggest that English readers, in part, may indeed read nonwords by using a strategy of reading them “by analogy” to real words.

Such differences between languages can even be found within the same person. In one study, bilinguals were asked to read pseudowords that were embedded either within the context of reading German, which has more consistent orthography, or within the context of reading French, which has a less consistent orthography. When read in the context of German, the pattern of electrophysiological activation was consistent with the use of a phonological route, whereas in the context of French, the pattern was more consistent with the use of a “by analogy” direct route (Buetler et al., [2014](#)).

How are we to understand the pattern of results across all of these studies of reading? As we have discussed, the set of regions involved in language is quite diverse and depends on what one is reading and the nature of the specific language (e.g., Italian versus English). This diverse pattern probably reflects the fact that there has been little or no evolutionary pressure to sculpt brain organization for reading. Rather, during reading the brain appears to cobble together processing modules that are important for other cognitive domains. For example, the process of identifying the form of words appears to rely on neural machinery that is important for object recognition, and the phonological analysis of items appears to rely, in part, on frontal regions involved in motor production of those sounds.

Not only does reading rely on a diverse set of regions, but it also appears to rely on the coordination between regions. Consistent with many models of reading, MEG studies suggest that visual word form regions are first activated at around 200 milliseconds after the presentation of a written word. Afterward, at about 400 milliseconds, activity is observed over both posterior regions (temporal, parietal) and frontal regions, including regions that support phonological processing as well as those that support semantic processing (Mainy et al., [2008](#)). (For a detailed review of the ERP markers that may index the early stages of processing of each of these routes, see Dien, [2009](#).) Moreover, MEG studies find that there is coupling in time of activity across these temporal and frontal regions (Salmelin and Kujala, [2006](#)). These findings highlight the fact that reading relies not only on particular brain areas, but also on the coordination between them. As discussed earlier with regard to auditory language, coordination of these processes occurs via white-matter tracts. The importance of these tracts for the integrity of the reading process is a recent focus of investigation especially as it influences the ability to acquire language skills (Wandell and Yeatman, [2013](#)). We return to this idea in [Chapter 15](#), in which we discuss developmental dyslexia, a disorder in which children have difficulty learning to acquire the skill of reading.

Before we leave the topic of reading, it should be noted that there is increasing interest in how learning to read influences the brain. In one fascinating study,

researchers traveled to Colombia, which, because of a decades-long civil war, had a population of rebels living in rural areas who had little or no formal schooling. As the conflict has been winding down, these people have become more integrated into society and, as a result, a number of them are learning to read at a relatively late age. Compared to people who have never learned to read (i.e., illiterate individuals), these “late literate” people exhibited more gray matter in a number of superior temporal and inferior parietal regions that have been implicated in the phonological route (see [Figure 8.16](#)). Because the groups were matched for overall IQ and other language abilities, such as naming words and repeating back numbers, it is likely that these neural differences reflect the impact of their experience with reading (Carreiras et al., [2009](#)).

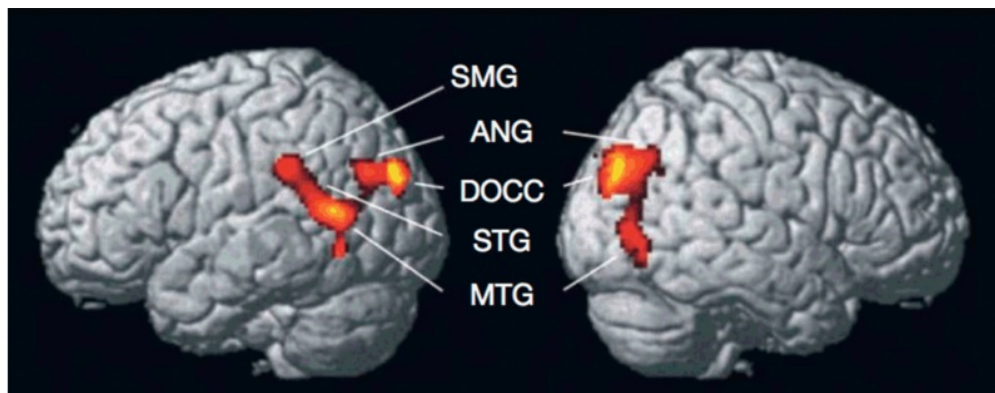


Figure 8.16 Brain regions that show increased gray matter in people who learned to read later in life compared to those who never learned to read.

Notice that these regions encompass many regions associated with the phonological route to meaning. (SMG= supramarginal gyrus, ANG = angular gyrus, DOCC = dorsal occipital gyri STG= superior temporal gyrus, MTG = middle temporal gyrus.

(from Carrerias et al., [2009](#))

Other research has shown that the integrity of the arcuate fasciculus, which connects posterior to anterior brain regions, is greater in adults who have become literate as compared to those who have remained illiterate. The integrity of these white-matter tracts does not differ between the late literate and literate individuals, presumably because both groups currently know how to read (Thiebaut de Schotten et al., [2014](#)).

Literacy may also change the function of specific brain regions. As you may remember from our discussion earlier, there is some debate as to whether the brain region that is responsible for processing the visual form of words is specifically engaged in processing words, or whether it is a region that becomes sensitive to words as a result of experience and repeated exposure. Findings suggesting the latter come from studies in which the sensitivity of the visual word form area to other visual stimuli, such as faces, is examined in across literate, late literate, and illiterate adults. As the sensitivity of this region to words increases with exposure to language, sensitivity to faces decreases (Dehaene et al., 2010) (see [Figure 8.17](#))! This finding suggests that indeed the function of brain areas is being sculpted by experience, a topic we discuss in more detail in the [next chapter](#) on memory and learning. (For review of the effects of literacy on the brain, see Dehaene et al., 2015.)

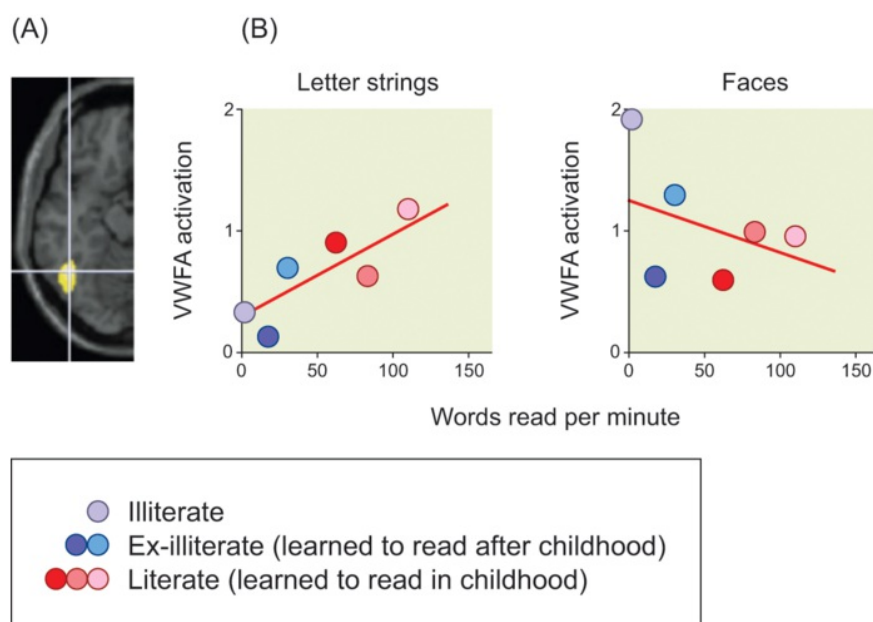


Figure 8.17 Changes in the organization of the visual word form area as a consequence of learning to read.

A) Shown here is the location of the visual word form area (VWFA). B) With increasing literacy, activity in the visual word form areas increases for letter strings (left) and decreases to faces (right).

(from Dehaene et al., 2015)

So far, all the evidence we have discussed regarding the neural bases of language has come from studies involving speakers and readers of Indo-European languages. We now turn our attention to other linguistic systems to provide more insight into the cognitive neuroscience of language.

Processing of Non-Indo-European Languages and Other Symbolic Systems

Many languages are used around the world, and some of these languages do not rely on the kind of phonological system that is used in English. By investigating the organization of the brain for other types of languages, we can determine the degree to which certain aspects of brain organization for language are universal.

Kana and Kanji

Because not all writing systems in the world use a phonetic alphabet based on phoneme-to-grapheme correspondences, as English does, cognitive neuroscientists can look to other language systems to investigate the distinction between phonological and direct routes to meaning. Japanese provides one such opportunity. It consists of two writing systems: one known as kana, which is syllabic and sound-based, and another, known as kanji, which is logographic and derived from Chinese (Paradis et al., [1985](#)).

In a syllabic writing system such as kana, each symbol is linked to a whole syllable rather than to an individual phoneme. For example, a syllabically based language might have a symbol for the sound “tor,” which would appear as the first of three symbols in a three-syllable word such as torrential, and the second of two symbols in the two-syllable word motor. Because syllabic systems are sound-based, these words can be read using a phonological route. In contrast, in a logographic writing system, such as kanji, each symbol stands for a concept, and the visual form of the word has no systematic relationship to how the word is pronounced. Typically, thousands of basic logographs are used in such languages; the reader must be able to associate each

different symbol with a different word. Logographic systems require a direct route because little or no information in the symbol provides hints as to its pronunciation. Some examples of kana and kanji characters are presented in [Figure 8.18](#).

| | | | | | | | | | | | |
|----|-----|----|----|----|----|-----|-----|----|----|--|--|
| ア | イ | ウ | エ | オ | カ | キ | ク | ケ | コ | | |
| a | i | u | e | o | ka | ki | ku | ke | ko | | |
| サ | シ | ス | セ | ソ | タ | チ | ツ | テ | ト | | |
| sa | shi | su | se | so | ta | chi | tsu | te | to | | |
| ナ | ニ | ヌ | ネ | ノ | ハ | ヒ | フ | ヘ | ホ | | |
| na | ni | nu | ne | no | ha | hi | hu | he | ho | | |
| マ | ミ | ム | メ | モ | ヤ | イ | ユ | エ | ヨ | | |
| ma | mi | mu | me | mo | ya | i | yu | e | yo | | |
| ラ | リ | ル | レ | ロ | ワ | ヰ | ウ | エ | ヲ | | |
| ra | ri | ru | re | ro | wa | i | u | e | o | | |
| ガ | ギ | グ | ゲ | ゴ | ザ | ジ | ズ | ゼ | ゾ | | |
| ga | gi | gu | ge | go | za | ji | zu | ze | zo | | |
| ダ | ヂ | ヅ | デ | ド | バ | ビ | ブ | ベ | ボ | | |
| da | ji | zu | de | do | ba | bi | bu | be | bo | | |
| パ | ピ | プ | ペ | ポ | ヴ | ン | | | | | |
| pa | pi | pu | pe | po | vu | n | | | | | |

| | | |
|---|--------------------|--|
| 甘 | "sweet" | |
| 感 | "be affected" | |
| 刊 | "print" | |
| 慣 | "be accustomed to" | |
| 観 | "view" | |
| 勘 | "investigate" | |
| 遅 | "slow" | |
| 管 | "tube" | |
| 環 | "a ring" | |
| 歓 | "enjoy" | |
| 巻 | "a volume" | |
| 韓 | "Korean" | |
| 漢 | "Chinese" | |

} "Kan"

Figure 8.18 Examples of kana and kanji.

(left) Almost all of the 77 symbols in kana represent a consonant-vowel combination. (right) In kanji, the symbol has little relation to how the word is pronounced. Pictured here are various symbols, all of which are pronounced "kan" but each of which has a different meaning.

After brain damage, the ability to read words in kana can dissociate from the ability to read words in kanji, implying a distinction between direct and phonological routes to meaning. Sometimes people who lose the ability to read kanji retain the ability to read kana, whereas other people who retain the ability to read kanji lose the ability to read kana (Sasanuma, [1980](#)). Furthermore, both case studies of patients with lesions (e.g., Kawamura et al., [1987](#); Kawahata et al., [1988](#)) and neuroimaging studies suggest that kana is primarily dependent on more dorsal regions of the left hemisphere, including the angular gyrus and temporoparietal junction, whereas the reading of kanji appears to rely more on inferior posterior temporal regions bordering on the occipital lobe (e.g.,

Sakurai et al., [2000](#)), consistent with reliance on the phonological route and the direct route, respectively. Although both scripts activate the visual word form area of the left hemisphere (Bolger et al., [2005](#)), other evidence suggests that because the nature of the scripts differ, they are also processed somewhat differently in ventral visual processing regions. Using direct electrical stimulation of the brain in patients with epilepsy, researchers have found that stimulation in different portions of the ventral visual processing stream interrupts the ability to read kana compared to kanji (Usui et al., [2009](#)). Despite these differences, neuroimaging studies suggest a substantial overlap of brain regions involved when reading either script (e.g., Ino et al., [2009](#)). These findings provide converging evidence from a language other than English that access to meaning through a sound-based reading system can be independent of access to meaning through a visually based system.

Music

Like language, music is an abstract symbolic system. Consequently, investigating how the brain processes music can provide insights into the basis of neural organization for language. If a region of the brain is active during language because it is specialized for processing an abstract representational system based on auditory information, such activation should be observed not only for language, but also for music. In contrast, if a brain region is truly specialized for language, then it should not be utilized when processing music. Data suggest that there may be some truth in both viewpoints (for a book length review, see Patel, [2008](#); for a review of brain systems involved in music, see Peretz and Zatorre, [2005](#)).

Case studies of patients show that amusia – a term used for acquired disorders of music perception, performance, and reading or writing following brain damage – can occur without the loss of language abilities. Conversely, aphasias can be exhibited without amusia (see Alossa and Castelli, [2009](#), for a discussion of amusia; and Stewart et al., [2006](#), for a longer discussion of disorders of musical listening). This double dissociation suggests that music and language are separable. In fact, melodic intonation

therapy, which relies on using speech within a melodic context, takes advantage of the fact that individuals with nonfluent aphasia are capable of singing words that they cannot speak (see Merrett et al., [2014](#), for a review).

Neuroimaging studies of brain activation related to reading suggest that different brain regions are used for reading words than music. As shown in [Figure 8.19](#), in musical notation, specific notes have particular spatial positions on the musical staff. The position of the note on the staff indicates how high or low its pitch is, and the distance between two notes indicates their difference in pitch. How much of the note is filled in and what kind of tail it has indicates the duration of that sound, providing information on rhythm.

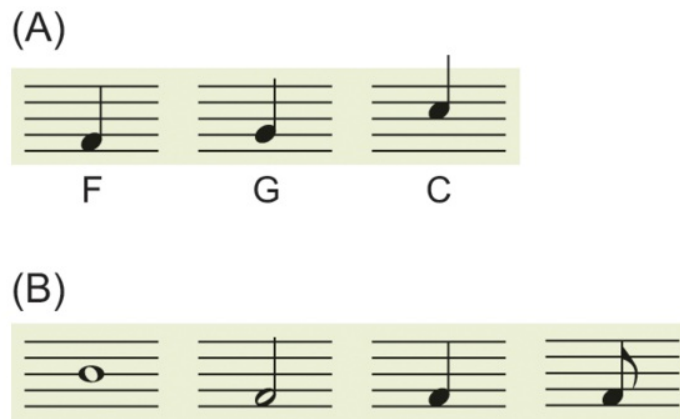


Figure 8.19 Spatial and rhythmic aspects of musical notation.

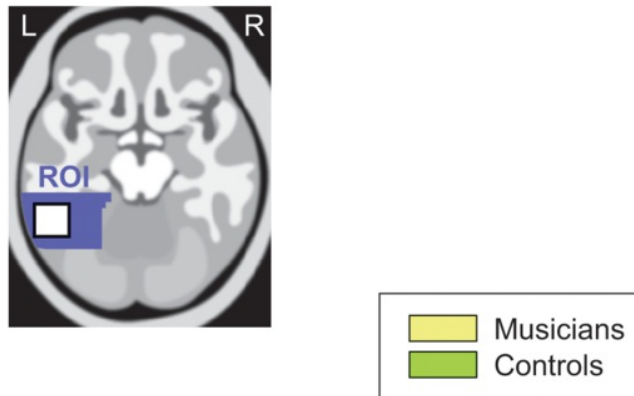
(A) In musical notation, each note has a particular location on the musical staff (which comprises five lines); either between two lines (as in the case of the notes F and C) or intersecting a line (as in the case of the note G). The higher the location, the higher the pitch (e.g., F at 343 Hz is lower in pitch than G at 384 Hz, which in turn is lower than C at 512 Hz). The relationship between the pitch of two notes is depicted in musical notation by the spatial distance between the notes. Because G is only slightly higher in pitch than F, it is located just a little above F; because C is significantly higher in pitch than G, it is located substantially above G.

(B) The duration of a note is indicated by both the body and the tail on the note. Notes that last longer in time have large bodies and are not filled, whereas those that are shorter have filled bodies and tails. Shown left to right are notes that could be held for 4 beats, 2 beats, 1 beat, and $\frac{1}{2}$ beat respectively.

One of the earliest studies to explore the brain regions involved in reading music used PET to compare activity when a person reads a musical score compared to looking at dots. This study found activity centered in the left occipitoparietal junction, in a region dorsal to that activated during the reading of language (Sergent et al., [1992](#)). Subsequent studies have more directly examined which regions of the ventral visual processing stream process words versus musical notation. While not surprisingly activity is observed in the visual word form area for words, the region that processes musical notation is somewhat lateral and posterior.

Furthermore, experience with musical notation may affect the organization of these visual processing areas. Earlier in the chapter we discussed how becoming literate as an adult appears to make the visual word form area less sensitive to faces. Similarly, experience with musical notation appears to shift the brain regions processing words. While the region processing musical notation is similar in musicians and nonmusicians, the brain region processing words is more distant in musicians, suggesting perhaps that the processing of musical notation encroaches on brain regions that normally would process words (see [Figure 8.20](#)). (See Benz et al., [2015](#), for a longer discussion of how musical training may affect different cognitive processes and their neurobiological substrate.)

(A)



(B)

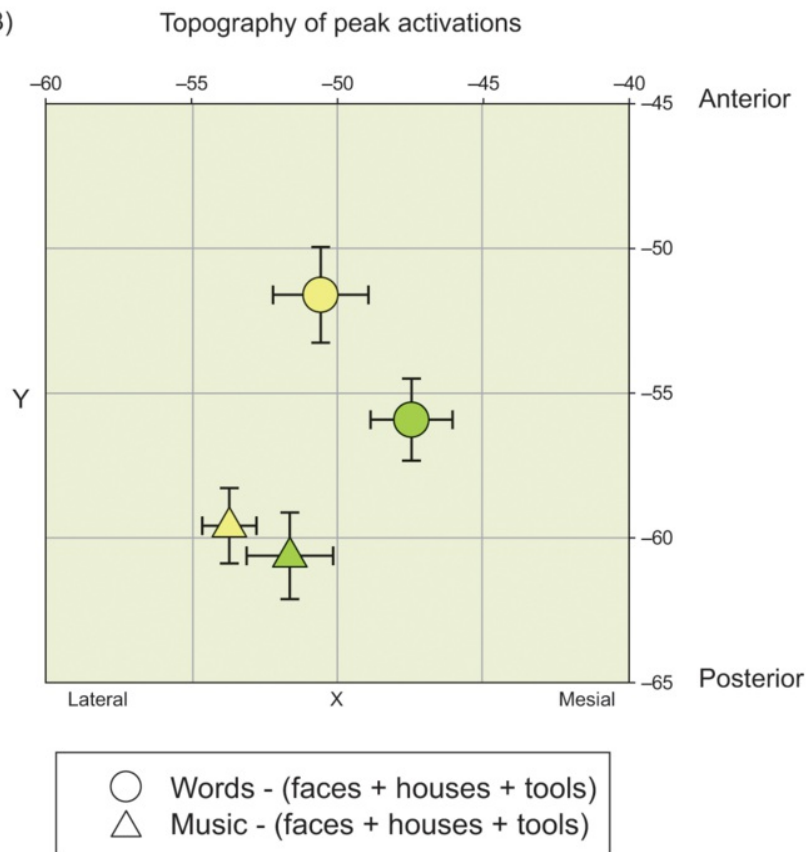


Figure 8.20 Changes in the location of the visual word form area as a result of significant musical training.

(A) Location of the region of interest (ROI), the visual word form area, shown in B. (B) While the brain region (triangles) that becomes activated when musicians (yellow) and non-musicians (green) reading musical symbols are located relatively near each other, the region that becomes activated for words (circles) is further away from that processing musical symbols in musicians than non-musicians. This pattern

suggests that learning to read musical notation has an impact on brain regions that are involved in decoding the visual symbols associated with words.

(from Mongelli et al., [2016](#))

We can also ask what brain regions are involved when one must translate musical notation into action. To examine this question, researchers looked at the brain activity of trained musicians when they had to play a note on a five-button keyboard based on musical notation of the note, as compared to a verbal label for the note or viewing the number of the finger that would be used to play that note. In this study, musical notation yielded greater activity than the other two methods of identifying notes in right occipitotemporal regions, which the authors suggested might be the right-hemisphere homologue of the visual word form area. They also observed more activity in the right supramarginal gyrus, which they suggested might be involved in translating a spatial notation to a motor pattern (Schön et al., [2002](#)). In sum, the spatial nature of musical notation appears to engage somewhat distinct regions of the left hemisphere and perhaps more right-hemisphere mechanisms than written language (see Stewart, [2005](#), for review).

However, these differences should not be overblown as they still suggest a role for the left hemisphere in reading musical notation. As one example to make this point, there is a fascinating case study of a professional opera singer who needed to undergo neurosurgery to remove a brain tumor (Riva et al., [2016](#)). Before surgery the doctors mapped those brain regions involved in reading musical scores, as obviously they did not want to impair his ability to do so. This study showed that his ability to read musical scores was disrupted by stimulation to left anterior temporal regions that we discussed earlier as being related to semantic processing, and by stimulation to the inferior frontal regions, which as we discuss next may be involved in syntactic processing not only in language but also in music.

In contrast to somewhat of a separation of brain regions required for reading language compared to reading music, other aspects may rely more closely on

overlapping regions. First, “syntax” processing in both language and music may rely on overlapping neural substrates. As discussed earlier, Broca’s area is important for detecting a violation of syntactic structure, such as when a word in a sentence makes it ungrammatical. Similarly, one can determine what brain region reacts when a chord is played out of sequence, as the expectation of typical sequences in music can be considered akin to the syntactic structure of language. As with language, MEG reveals a component elicited by a chord in an anomalous position. It occurs approximately 200 ms after presentation of the chord, with dipole modeling indicating a source located in Broca’s area (see [Figure 8.21](#); Maess et al., [2001](#); see Fadiga et al., [2009](#), for a recent discussion).

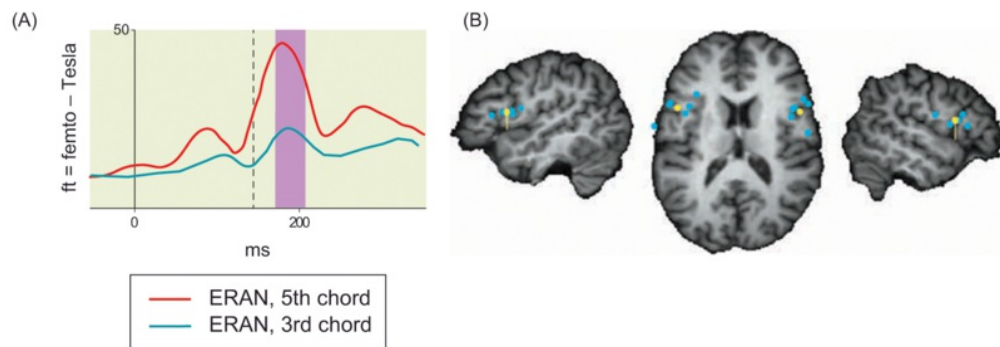


Figure 8.21 Early right anterior negativity (mERAN) as recorded using MEG.

(A) Notice that the negativity is greater to an anomalous chord, the Neapolitan fifth, as compared to a standard chord, the third (adapted by permission from Macmillan Publishers, LTD: Maess, B., Koelsch, S., Gunter, T. C., Friederici, A. D., *Nat Neurosci.* 2001 May, 4(5): 540–545. Figure 5, page 54). (B) The average source of the ERAN, shown in yellow. Note that it is located in Broca’s area. The individual locations for each participant in the study are shown in blue.

The location of this activation in frontal regions is consistent with the idea that the overlap in the processing of language and music occurs because they rely on similar executive control processes that help to prioritize and organize information in working memory (Slevc and Okada, [2015](#)). It may be that rhythm, both in speech and musical processing, helps to denote or highlight important information, and that the structure of

rhythm helps to predict the type of “syntactic” frame in which information is embedded (Jung et al., [2015](#)). In the end, it should not be surprising that music and language share at least some overlapping neural systems, as they both are systems that humans use to communicate their intentions, their thoughts, and also, importantly, their feelings (Kraus and Slater, [2016](#)) .

Right-Hemisphere Contributions to Language Processing

Since Broca, the role of the left hemisphere in language has been considered so central that this hemisphere is often referred to as the verbal hemisphere. However, more recently researchers have come to appreciate that the right hemisphere is not a silent partner in language processing. Thus, we next turn our attention to the ways in which the right hemisphere contributes to language processing (for reviews, see Lindell, [2006](#); Jung-Beeman, [2005](#)).

As we discussed in this chapter and in [Chapter 2](#), the right hemisphere of split-brain patients can comprehend written and auditory language, but its abilities are limited. It has a poor understanding of complicated syntax, cannot produce speech or use phoneme-to-grapheme correspondence rules, and has a vocabulary restricted mainly to concrete words as opposed to abstract words.

Despite these limitations, the right hemisphere contributes to the extraction of meaning from linguistic material in three main ways. First, the right hemisphere is involved in processing certain aspects of [prosody](#), which is the intonation pattern, or sound envelope, of an utterance. Second, the organization of semantic information in the right hemisphere differs from that of the left, providing a broader scope from which individual words are considered. Third, the right hemisphere plays an important role in narrative and inference. [Narrative](#) refers to the ability to construct or understand a story line, whereas [inference](#) refers to the ability to “fill in the blanks” and make assumptions about material that is not explicitly stated (i.e., material that is implied). In

all cases, the right hemisphere's contribution can be characterized as providing a broader lens on language processing that extends beyond the consideration of linguistic material on a word-by-word basis to the larger context.

Prosody

Prosody, the sound envelope around words, can be useful in providing information about interpretation of a statement. For example, in English, a declarative statement is usually accompanied by a decrease in the pitch of one's voice, whereas a question is usually accompanied by a rising intonation pattern. In some cases, intonation pattern may be the only cue allowing one to differentiate between two interpretations of an ambiguous sentence. Consider how prosody could differentiate the meaning of the four words "She did it again" as a response in the following dialogue:

LYNN: After all her injuries, you would think that Alice would be a bit more cautious.

But yesterday, she followed me down a very steep ski run and took a bad tumble.

SARA: She did it again.

If said with a rising intonation, Sara is asking whether Alice hurt herself again. In contrast, if Sara said these same words emphatically with a falling pitch (e.g., "She did it again!"), the intonation would indicate that she is asserting what she already knows: Alice has managed to injure herself once more.

The idea that the right hemisphere plays an important role in interpreting prosodic cues (e.g., whether a tone of voice is warm and friendly, sarcastic, condescending, or excited) was originally revealed in studies performed decades ago with split-brain patients, individuals with unilateral brain damage, dichotic listening studies, and individuals undergoing the Wada test (e.g., Benowitz et al., [1983](#)). At that time, researchers considered the possibility that perhaps this right hemisphere's involvement in processing prosody occurred because, as we will learn in [Chapter 12](#), it is specialized for interpreting emotional signals in voice and facial expression. However,

researchers found that a right-hemisphere role in understanding prosody is not limited to situations in which prosody implies an emotional state (e.g., a brief high-frequency monotone might imply surprise) or a speaker's attitude (e.g., confidence, politeness) (Pell, [2006](#)). It can also be found when prosodic information is emotionally neutral (i.e., rising and falling intonation contours) (e.g., Weintraub et al., [1981](#)).

The right hemisphere's organization for interpreting prosody may parallel that of speech perception in the left hemisphere, with both a dorsal route that connects posterior temporal to premotor and inferior prefrontal regions, and a ventral route that connects posterior to anterior superior temporal regions. Supporting this viewpoint, TMS over right inferior frontal regions disrupts the ability to interpret prosodic cues (Sammler et al., [2015](#)).

Yet, this evidence should not be taken to suggest the left hemisphere is uninvolved in interpreting prosody. Rather, neuroimaging evidence suggests that, at least with regards to prosodic cues in linguistic utterances, the right hemisphere may not be a leader as much as a partner with the left hemisphere (Witteman et al., [2011](#)). And while a meta-analysis of activation in neuroimaging studies in tasks involving linguistic prosody showed strong activation in posterior regions of the right hemisphere, a homologous site in the left hemisphere also consistently exhibited activation, albeit not to as great an extent (Belyk and Brown, [2014](#)).

Up until now we have been focusing on the interpretation of prosodic cues. What about their production? Once again, evidence seems to suggest that the hemispheres make distinct but parallel contributions. Prosody consists of two classes of cues: those related to pitch or tone and those related to timing. Consistent with a right-hemisphere superiority for tonal processing, [aprosodic](#) speech, in which an individual speaks all at one pitch, is observed after damage to anterior regions of the right hemisphere (Behrens, [1988](#)). As such, the right hemisphere's organization for prosody appears to mimic that of the left hemisphere for language, with a distinction between anterior regions involved in production and posterior regions involved in perception (Ross and Monnot, [2008](#)).

After damage to the left hemisphere, speech is not so much aprosodic as **dysprosodic**, meaning that it has disordered intonation. The dysprosodia seems to result from the ill-timed prosodic cues consistent with a left-hemisphere superiority for temporal aspects of processing. For example, neurologically intact individuals tend to elongate the final word rather than the initial word of an utterance. In contrast, persons with Broca's aphasia do the opposite, elongating the first word rather than the last (e.g., Danly and Shapiro, [1982](#)).

Semantics

One way in which the right hemisphere may contribute to language is by gaining access to the meaning of words in a different manner than its partner. Experts have known for some time that when we hear or read a specific word, such as nurse, it primes our ability to process a network of words related in meaning, such as doctor, hospital, needle, and so forth. Back before neuroimaging studies were possible, divided visual field studies demonstrated that the network of associated words that gets primed by a given word is more restricted in the left hemisphere than in the right. For example, whereas the right hemisphere retains activation of both meanings of an ambiguous word (e.g., bank) for about 1 second, the left hemisphere retains only the dominant meaning (e.g., "repository for money"), not the subordinate one (e.g., "side of a river") (e.g., Burgess and Simpson, [1988](#); Chiarello, [1991](#)). Furthermore, weakly related words facilitate the processing of a word presented in the left visual field but not a word presented in the right visual field (e.g., Rodell et al., [1992](#)).

These results could suggest that there are parallel semantic processing systems in each hemisphere. Whereas fine semantic coding by the left hemisphere allows information occurring close together in a sentence to be integrated, the coarser and more diffuse semantic processing of the right hemisphere has been suggested to play an important role in integrating information over larger linguistic expanses (Jung-Beeman, [2005](#)). Supporting this idea, there is greater right hemisphere activation when an individual must generate a word to finish off a sentence that has many possible endings

(e.g., “He went into the house, garden, bank, office, store), than when there is one likely ending (Kircher et al., [2001](#)).

A somewhat different but related conceptualization has been provided by ERP studies (e.g., Federmeier, [2007](#)). This model suggests that the right hemisphere’s interpretation of a given word is broader and more “context-free” in comparison to that of the left hemisphere. In contrast, the left hemisphere is actively predicting what type of word is likely to occur in a sentence based on a number of different linguistic cues, such as the syntactic structure in which the word is embedded, the prior words in a sentence that may have been seen or heard, and so forth. As such, the left hemisphere will focus in on a particular interpretation of information, excluding others. The right hemisphere’s ability to hold onto the meaning of a word without being biased by such information is important when linguistic information must be reconsidered or reanalyzed, such as in garden path sentences in which the sentence initially appears to mean one thing but then actually means another. What is common to both these models is that they posit that by having different ways of processing semantic information, each hemisphere can make a parallel but important contribution to language (e.g., Wlotko and Federmeier, [2013](#)).

Narrative, Inference, and Metaphor

Although when we think of language, we often focus specifically on words themselves, the interpretation of language relies on cues that spans not only across words, but also sentences. As just a simple example, consider the case of anaphora, in which there is a grammatical substitute, such as a pronoun, to refer to a preceding word or group of words. If you read the sentences “John did not know what to make of Susan’s response. He wondered about the meaning of her curt reply”, you understand that “He” in the second sentence refers to John.

Moreover, to comprehend language, we superimpose structure upon discourse. This structure allows us to organize information so that clauses within sentences, or episodes or events within stories, can be linked to one another, and so that material is presented

in an orderly fashion, building upon that presented previously. Individuals with right-hemisphere damage can have difficulty building such structures such as ordering sentences so that they form a story (e.g., Delis et al., [1983](#)), and determining whether an utterance is relevant to a conversation (i.e., determining whether it builds upon previously presented material) (e.g., Rehak et al., [1992](#)). They may also have difficulty extracting or following the theme of a story (e.g., Moya et al., [1986](#); Kaplan et al., [1990](#)), or using information about a story's theme to help them in other tasks, such as arranging sentences into coherent paragraphs (e.g., Schneiderman et al., [1992](#)). In addition, they may have difficulty in making inferences based on what has been previously said (e.g., Beeman, [1993](#)). For example, consider a story about a person walking barefoot along the water's edge on a beach. The story describes how the beach is frequented at night by teenagers who drink beer there and then smash the bottles for entertainment. And then the story notes that the person feels a sharp pain in his foot and notices that it is bleeding. While most of us would make the inference that this person has stepped on broken glass, patients with right-hemisphere damage are less likely to do so. Participation for the right hemisphere in processing discourse appears to occur even in visual languages, as inferred from as case reports of deaf signers with right-hemisphere damage (Hickok et al., [1999](#)).

One interesting ramification of an inability to comprehend a coherent theme in stories is that it makes it difficult to comprehend jokes. Certain researchers have suggested that jokes are funny because most of a joke forms a coherent story, but then the punch line contains a surprise or twist that nevertheless coheres with the overall story. Given that individuals with right-hemisphere damage have difficulty following the thread of a story, it is not surprising that they have difficulty selecting the correct punch line for a joke. They are likely to pick a surprising ending but not one that is compatible with the previously presented material (e.g., Brownell et al., [1983](#)).

Converging evidence for the role of the right hemisphere in understanding discourse is provided by neuroimaging studies. Activation of the middle temporal gyrus of the right hemisphere is observed when individuals are told to pay attention to the general

theme or moral of one of Aesop's fables, as compared to being asked specific information about an attribute of a fable character (Nichelli et al., [1995](#)). Likewise, this area is more activated when individuals read an untitled paragraph and have to deduce its main theme, compared to reading a paragraph when the title provides such information (St. George et al., [1999](#)). Once again, that is not to say that the left hemisphere makes no contribution to such processes. Rather, a meta-analysis of neuroimaging studies of text comprehension found consistent bilateral activation in anterior temporal regions (Ferstl et al., [2008](#)) and other researchers have found robust bilateral patterns of activation in more posterior temporal regions as well (AbdulSabur et al., [2014](#)). In addition, neuroimaging studies reveal bilateral activation when comprehending either verbal jokes (Goel and Dolan, [2001](#)) or jokes presented in nonverbal form, such as cartoons (e.g., Bartolo et al., [2006](#); Mobbs et al., [2003](#)).

There are also times in which we use words in a nonliteral manner, such as in metaphors, idioms, and indirect requests. While we still can extract the speaker's or writer's meaning, people with right-hemisphere brain damage have difficulty doing so (e.g., Brownell, [1988](#)). For example, individuals with such damage may be horrified to hear that someone was "crying her eyes out" because they interpret the sentence literally, and thus visualize a gruesome scene. When asked to point to a picture of someone who has a "heavy heart," an individual with right-hemisphere brain damage is likely to point to a picture of a large heart rather than to a picture of someone who looks sad (Winner and Gardner, [1977](#)). When given a sentence such as "Can you open the door?" a person with this type of brain damage might respond defensively, saying, "Of course I can open the door. Why do you ask? Do you think I'm such a weakling that I can't even open a door!?", when what was really meant was "Please open the door for me" (e.g., Foldi, [1987](#)).

Neuroimaging studies are consistent in that processing metaphorical aspects of language leads to changes in activation in the right hemisphere, most notably the middle temporal gyrus and the frontal pole (e.g., Bottini et al., [1994](#)). Yet once again, other

neuroimaging evidence suggests that the right hemisphere is working in parallel with the left, in this case to process metaphor (e.g., Obert et al., [2014](#); Lai et al., [2015](#)). Some researchers have suggested that the more novel or unexpected a metaphor is, the more likely one is to see right-hemisphere involvement. They posit that this pattern would occur because right-hemisphere mechanisms are required to make inferences about what the metaphor means and/or to integrate such information, especially within the ongoing theme or context (Diaz and Hogstrom, [2011](#)). Others have argued that comprehending metaphors is demanding, and, as such, additional brain resources beyond those in the left hemisphere must be brought to bear to enable understanding (Prat et al., [2012](#)).

Even though from the time of Broca, language has been thought of as the domain of the left hemisphere, language relies on an entire brain and its interacting parts, not just one hemisphere. This conclusion was brought home by a relatively recent meta-analysis of brain activation across numerous studies investigating different aspects of language functioning, such as phonology, syntax, and semantics. Right-hemisphere activation was observed for most language tasks, although not necessarily to the same degree as that of the left. This evidence suggests that the right hemisphere provides a helping hand in language processing. Nonetheless, in the case of sentence and text processing, the right hemisphere was consistently activated to a greater degree than the left. This greater activation was noted in right temporal regions involved in semantics (Vigneau et al., [2011](#)).

Integrating all we have discussed, the right hemisphere appears to bring a richness to our understanding of language. Although damage to the right hemisphere will not so severely disrupt the ability to comprehend language and convey meaning, the aspects of language that we may find most appealing, such as a wonderful metaphor or an unexpected twist or turn of phrase, might not be quite so well appreciated or in other cases may be left unsaid.

Summary

Neurological Bases for Auditory Language Processing

- The Wada test, in which one hemisphere is anesthetized, provides evidence of left-hemisphere specialization for speech output in all but a fraction of right-handers.
- A breakdown in language functioning after brain insult is known as aphasia.
- Anterior regions of the left hemisphere, more specifically Broca's area, classically have been considered to be specialized for speech output.
- Posterior regions of the left hemisphere, most notably Wernicke's area, classically have been considered to be specialized for speech comprehension.
- Phonology, which refers to the rules by which sounds in a language are formed and the rules by which they can be combined, is disrupted in both anterior and posterior aphasias.
- Syntax, which refers to the rules of grammar dictating the ways in which words are conjoined to form sentences, is disrupted more in anterior aphasias.
- Semantics, which is the aspect of language that specifies meaning of words and sentences, is disrupted more after damage to posterior regions of the left hemisphere.
- Double dissociations seem to suggest distinctions between speech perception and speech output, as well as differences between the neural processing of phonology, semantics, and syntax.
- More recent evidence, while supporting these divisions in broad-brush strokes, has suggested that receptive language processing occurs in a more network-like manner rather than relying on specific regions for specific functions. This research suggests that interactions among brain regions support language processing with a more dorsal stream supporting phonological and motoric

processing and a more ventral stream involved in more word-level and semantic processing.

Visual “Spoken” Language

- The generality of the organization of language as deduced from studies of speech comprehension and speech production can be investigated in which information is conveyed visually by hand symbols rather than auditorily by sounds.
- In one such language, American Sign Language, syntax is marked not only by word order, as in English, but also by the spatial location where a symbol is made and by the type of hand movement.
- ASL seems to rely on similar regions of the left hemisphere as spoken languages, although the right hemisphere may play a somewhat larger role.

Neurological Bases for Visual Language Processing

- Alexia is the loss of reading ability as a result of a brain insult, while agraphia is the loss of the ability to write as a result of brain damage.
- The phonological route to meaning links the orthography (graphic form) of a word to its phonology (sound), which is then linked to meaning. This route is required for words one has never encountered and for nonwords (e.g., glimp) that could be real words but are not, and is lost in phonological alexia.
- The direct route links the orthography directly to the meaning. It is used to read irregular words, such as “colonel,” that do not follow the typical grapheme-to-phoneme correspondence rules, and is lost in surface alexia.
- People with phonological agraphia cannot spell using phoneme-to-grapheme correspondence rules, while people with lexical agraphia cannot spell using the direct route.
- Neuroimaging and ERP studies suggest that early visual identification of words

occurs in a specialized word form area in the fusiform cortex around about 200 milliseconds post-presentation.

- From there analysis of the written word appears to rely on two somewhat separable routes. As in receptive language, there is a dorsal route that is more involved in phonological aspects of reading, and a ventral route that is more involved in semantics.
- Also as in receptive language, the route that is utilized may be influenced by different factors. These include task demands, the nature of the language (whether most words follow standard symbol-to-sound translations or not), and a person's degree of literacy.

Processing of Non-Indo-European Languages and Other Symbolic Systems

- Kana is a syllable-based system in which each symbol is related to sound, much like the alphabetic system in English, and therefore can rely on the phonological route.
- Kanji is a logographic system, in which the symbol for each word is unique, and relies on the direct route.
- Evidence from both brain-damaged patients and brain imaging suggests that these two systems are dissociable.
- The reading of music and the reading of words rely on similar, but distinct, regions of the left hemisphere, suggesting that these activities are somewhat separable.

Language and the Right Hemisphere

- The right hemisphere activates a more diffuse and remote set of semantic associations than the left hemisphere, and those independent of current context. This organization can aid in discourse.

- The right hemisphere also contributes to the perception and production of prosodic cues, which are the intonation contour and timing parameters of speech that help disambiguate the meaning of utterances.
- The right hemisphere plays a major role in discourse by aiding a person in comprehending a story line, extracting the main theme or moral of a story, and making inferences based on previously presented material. It also aids in the nonliteral usage of language, such as metaphor.

Chapter 9

Memory and Learning



[What is Memory?](#)

[Hippocampal Damage Causes Amnesia, a Disorder of Long-Term Memory](#)

[Global Nature of the Deficit](#)

[Temporal Profile of Affected Memories](#)

[Spared Abilities](#)

[Spared Working Memory](#)

[Spared Skill Learning](#)

[Multiple Memory and Learning Systems](#)

[What Distinguishes Memory Systems?](#)

[Memory and Consciousness](#)

[Nonhippocampal Regions Involved in Memory and Learning](#)

[Domain-Specific Neocortical Regions: Initial Processing and Subsequent Access](#)

[The Basal Ganglia: Skill Learning](#)

[The Amygdala: An Interface Between Memory and Emotion](#)

[Anterior Temporal Regions: Amodal Storage of Semantic Information](#)

[Brain Systems for Different Stages of Memory](#)

[Encoding: The Medial Temporal Lobe and Prefrontal Regions](#)

[Consolidation and Storage: How Critical Is the Hippocampus?](#)

[Retrieval: Hippocampal, Prefrontal, and Parietal Mechanisms](#)

[The Role of the Hippocampus in Retrieval](#)

[The Role of the Prefrontal Cortex in Retrieval](#)

[The Role of the Parietal Cortex in Retrieval](#)

[In Focus: Does Sleep Help You to Remember?](#)

[Working Memory: The Ability to Hold and Manipulate Information On-Line](#)

[Patients With Deficits in Working Memory](#)

[Studies With Nonhuman Animals: A Role for Prefrontal Cortex?](#)

[Insights From Neurologically Intact Individuals](#)

[The Relationships Between Memory Systems](#)

[Theoretical and Computational Reasons for Distinct Memory Systems](#)

[Interacting Memory Systems for Different Types and Stages of Learning](#)

[Summary](#)

In response to a seizure disorder that could not be controlled effectively by anticonvulsant medications, in 1953 a young man underwent an experimental surgical procedure that removed medial temporal lobe structures that we now know are critical to memory. Although the surgery was successful in bringing the seizure disorder under control, it resulted in a profound deficit in memory. After the surgery, this man was unable to remember the events of his life or the people he met after the surgery, such as his physicians and other caregivers, or to learn new facts about the changing world around him. After the surgery he could not tell his age, the current date, or any aspect of his recent history (such as where he was living and how long he had lived there). In fact, on occasion in his later years, he misidentified a current picture of himself as a picture of his father. His memory was no better for people in the public eye or the public events in which they figured. Such deficits persisted until his death in 2008 at the age of 82.

Nevertheless, throughout his life, he still expressed a wide range of memory abilities. He could reason and solve problems, recognize objects, and perform

voluntary and reflexive motor acts appropriate to all manner of objects and situations. These abilities, along with his full range of linguistic skills, demonstrated that he could access the considerable store of knowledge that he had acquired early in life before the surgery. His ability to remember the remote past prior to his surgery seemed largely intact, as was his ability to hold information in memory temporarily while working with it, as long as he was not interrupted.

Because of the mixture of memory loss and memory retention, his life had some surreal qualities. For example, he enjoyed solving crossword puzzles and could happily do the same crossword puzzle over and over again, because he didn't notice the repetition. Although he also enjoyed watching television shows, they were difficult for him to understand because the commercials interspersed throughout a show caused him to forget the story line. He could also hold a perfectly reasonable conversation, except that his conversation was devoid of current content; he could not tell you about recent weather conditions or the books that he had most recently read. If you avoided such topics in your conversation with him, you would be hard-pressed to notice any memory deficit at all. However, if you left for a short while, even for only a few minutes, upon returning you would find that he could not remember what you had been conversing about minutes earlier, and, most likely, he could not remember having ever met you!

What was nearly as striking as his near-total inability to recollect his experiences was his intact ability to be affected by his experiences. Remarkably, he was able to acquire and express a variety of new skills, such as learning how to read words backward. He did so despite being unable to remember that he had ever been asked to read such words. Moreover, like neurologically normal individuals, his improvement in performance with practice was larger for the items he had previously seen than for new items presented for the first time. But the improved performance with repeated items occurred despite the fact that he

was unable to judge which items were the repeated ones and which ones were new.

The patient in the opening vignette of this chapter is known in the scientific literature by his initials, H.M. After realizing the unintended effects of the operation, his surgeon, Dr. Henry Scoville, contacted Brenda Milner and her colleagues at McGill University in Montreal to unravel the mystery of his memory loss. Professor Milner discovered the divide in H.M.'s memory that we just discussed: the paradox that while certain aspects of memory were lost after removal of his medial temporal lobe, others were retained (Scoville and Milner, [1957](#)). This work was critical in demonstrating the existence of at least two separable systems that support our ability to remember. As noted by Eric Kandel, who won the Nobel Prize in Physiology and Medicine in 2000 for his work on the molecular mechanisms involved in memory formation, “[t]he study of H.M. by Brenda Milner stands as one of the great milestones in the history of modern neuroscience. It opened the way for the study of the two memory systems in the brain, and provided the bases for everything that came later.”

H.M.'s contribution to our understanding of memory did not stop there. Over the next five decades, H.M. graciously participated in scientific studies conducted by Prof. Milner, and also by her former student Prof. Suzanne Corkin at MIT. These studies exhaustively documented his impairments and the abilities that he retained (e.g., Milner et al., [1968](#); Corkin, [2002](#) for a timeline of the major scientific landmarks in the study of H.M.; Squire, [2009](#)). H.M.'s memory loss is known as [amnesia](#), which in his case was remarkably profound and pervasive (see [Figure 9.1](#)). Amnesia includes loss of memory for materials such as words, text, names, faces, spatial layout, routes, geometric shapes, nonsense patterns, tunes, tones, public events, and personal episodes. H.M.'s amnesia apparently affected all aspects of his life and caused him to forget the events of his daily life “as quickly as they occur[red]” (Scoville and Milner, [1957](#), p. 15). Ironically, although H.M. is undoubtedly the most famous and intensively studied patient in the

annals of neurology, neuropsychology, and cognitive neuroscience, his memory impairment was so severe that he had no idea of his fame.

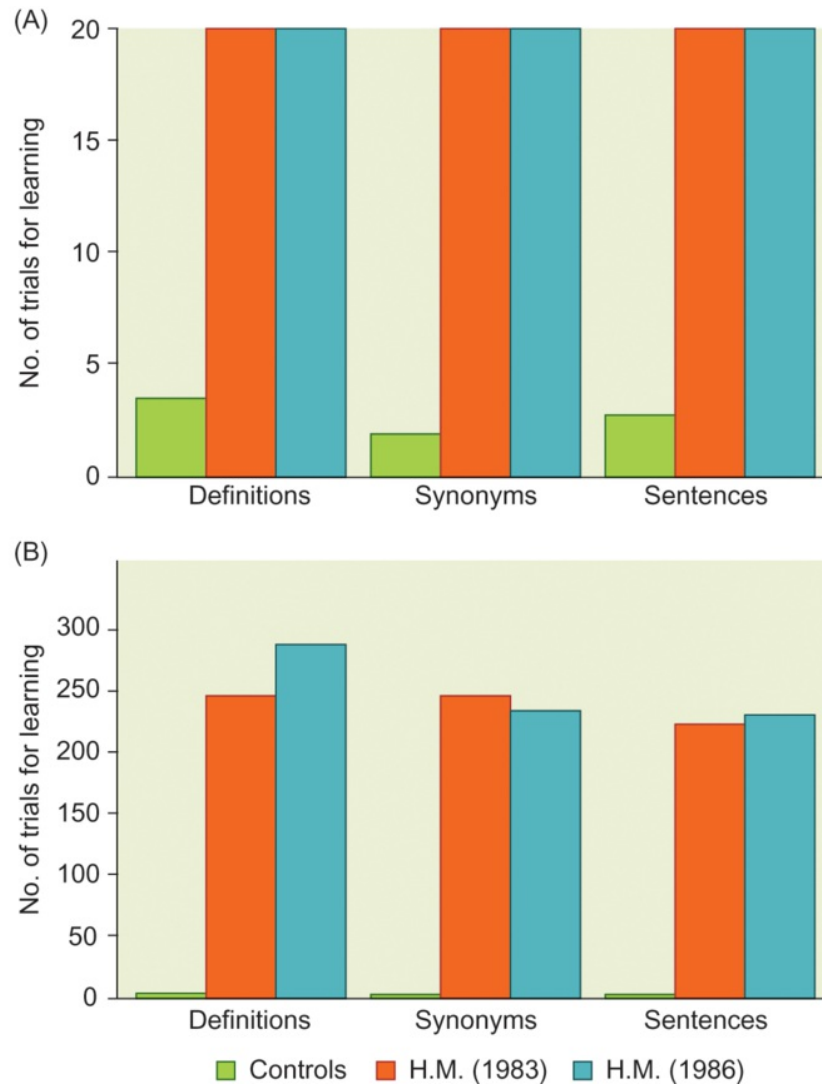


Figure 9.1 Illustration of profound inability of H.M., a patient who underwent bilateral removal of the temporal lobe, to acquire new information.

In this study (Gabrieli et al., [1988](#)), H.M. and neurologically intact control subjects (controls) were taught the definitions of vocabulary words that they did not previously know. (A) This graph depicts the number of trials required to meet the learning criterion. Note that when tested in both 1983 and 1986, H.M. received the maximum number of trials, 20, whereas the controls could learn the definitions, synonyms, and appropriate sentence frames for words in fewer than five trials. (B) In learning to select either the appropriate definition, the appropriate synonym, or the correct sentence frame for these vocabulary words, controls showed almost no errors, whereas H.M. made more than 200 errors in each case, never learning any of the words!

The disorder of memory seen in H.M. and in numerous other cases of amnesia, studied by various investigators in the field, tells us much about what memory is and how the brain manages to record our past experiences. Because memory can be compromised in apparent isolation from other cognitive abilities, amnesia demonstrates a basic functional independence of memory from other cognitive capacities. Because amnesia can be so selective, affecting only certain memory capacities while leaving other aspects of memory fully intact, it indicates that there are different kinds of memory. Like other functions we have discussed in this book, memory must be thought of as a collection of abilities supported by a set of brain and cognitive systems that operate cooperatively, each system making different functional contributions. Normal memory performance involves various systems, which ordinarily operate together so seamlessly that it is difficult to gain any intuitive appreciation of the separateness of the contributions made by the various systems. Only through careful and converging neuropsychological, neuroimaging, psychophysiological, and neurophysiological studies can we infer the distinct roles and contributions of the various brain and cognitive systems that collectively mediate memory. This chapter lays out our current understanding of the different systems and their functional roles.

What Is Memory?

We begin our examination of memory by posing the most basic question right from the start: What is memory? Perhaps the best answer to this question is that memory is the group of mechanisms or processes by which experience shapes us, changing our brains and our behavior. Tennessee Williams said, “Life is all memory except for the present moment that flies by so quickly we can hardly catch it going by.” For our purposes, memory is the ability to capture each successive “present moment” within the nervous system so that we are forever changed by it. How and where memory is captured within the nervous system is what we need to understand.

We can also ask, what is memory for? To this question there are many answers: Memory holds onto the details of everyday life; remembering to take our keys, coat, or lunch; recalling where we parked the car, left our backpack, or placed the groceries; remembering scheduled appointments, class assignments, or plans for the evening; and knowing the names, appearance, and defining characteristics of people we have met. But memory also holds information in mind for just a short time while we work on it, such as doing mental arithmetic. Memory is also for remembering the events of our lives and the people who inhabit them, and for identifying, appreciating, and responding appropriately to various objects and situations and the interactions among them. Moreover, memory captures the regularities in the world – the correlations and patterns of co-occurrence (of the letter combinations we type, of sights and sounds of related objects, or of smells and tastes of common foods) – and adapting our brains and behavior in accordance. Finally, more recent evidence suggests that memory also helps us to use the past to imagine the future.

However we look at it, memory encompasses a large collection of capabilities that share a common label. The brain, in accomplishing memory, must perform all these different capabilities. To do so requires a set of mechanisms supported by a set of brain systems. We turn now to identifying and characterizing those systems and the roles they play.

Hippocampal Damage Causes Amnesia, a Disorder of Long-Term Memory

Much of what we know about the cognitive neuroscience of memory has come from case studies of patients with memory disorders and from one particular form of memory disorder, namely, amnesia (see Rosenbaum et al., [2014](#), for review). Although now complemented by other approaches, the study of amnesia has provided scientists with fundamental insights into how the brain supports memory. Because this work has been so influential, we begin our examination of memory in the brain by discussing amnesia.

We will point out particular features of memory loss in amnesic syndromes and then consider how those pieces of data inform neural models of memory.

Although our discussion includes cases of amnesia resulting from varying etiologies, we will focus on the most famous case, H.M. Scientists learned an incredible amount from studies with H.M. for a number of reasons. First, H.M. generously participated in hundreds of studies over more than five decades. Second, the fact that H.M.'s amnesia resulted from a surgical resection was crucial. Remember, H.M.'s surgery occurred in the 1950s, well prior to the development of technology for CT or MRI scans of the brain. In those days, there was no way to clearly identify the structural damage to the brain in a given neuropsychological patient. But in H.M.'s case, the surgeon wrote specific notes on which structures he had excised so researchers knew specifically which structures were lesioned. It was discovered decades later on postmortem examination of H.M.'s brain that although the surgeon's notes made at the time of his operation were quite accurate, they did not perfectly capture the extent of the actual lesion, underestimating it in certain regards and overestimating it in others (Annese et al., [2014](#)). In addition, researchers knew exactly which aspects of memory had been impacted by the surgery, because H.M. had been evaluated prior to the surgery that left him amnesic. As a result, scientists learned invaluable information about the role of the hippocampus in memory from H.M.

The case of H.M. was the first to indicate that amnesia results from extensive damage to the regions of the medial temporal lobe, including the hippocampus, dentate gyrus, subiculum, amygdala, and neighboring parahippocampal area (the parahippocampal, entorhinal, and perirhinal cortices) (see [Figure 9.2](#)). Subsequent work with patients has confirmed that a critical structure involved in amnesia is the hippocampus, regardless of how that damage is sustained – whether by surgical resection, as with H.M., or any of a number of other etiologies, such as those involving loss of blood supply to the region, as in stroke or as a result of anoxia, or in certain disease processes that target this region, as in herpes simplex encephalitis. The

hippocampus is aptly named from the Greek for “seahorse,” because it is indeed shaped like one (see [Figure 9.3](#)). Information from a variety of different brain regions all converges in the adjacent entorhinal cortex to enter the hippocampus. Information then courses in a relatively unilateral manner and exits either by returning back to the entorhinal cortex or projecting to other brain regions via the fornix (see [Figure 9.4](#)). As we will learn later, this neuroanatomical architecture is important in understanding the functions of the hippocampus.

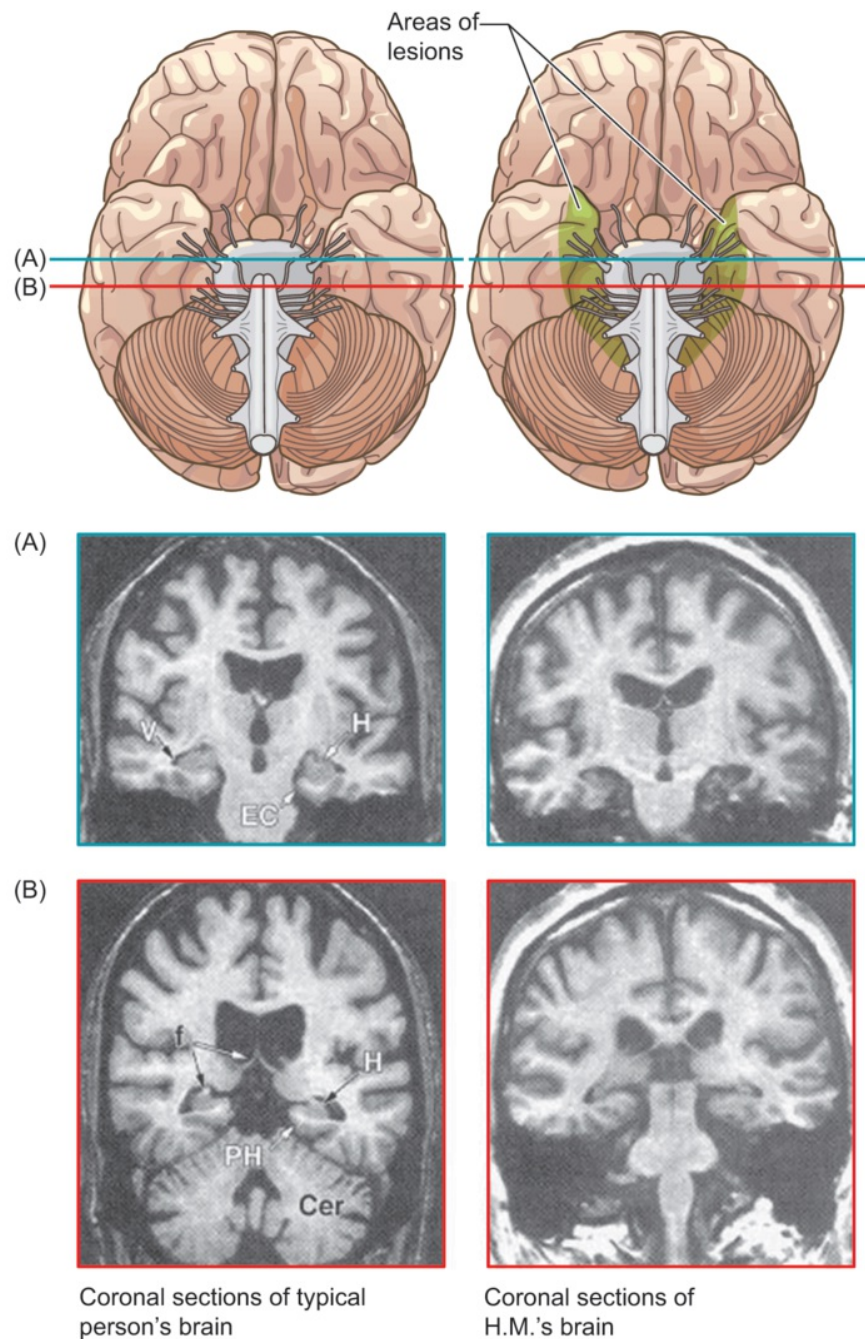


Figure 9.2 Brain structures removed during H.M.'s surgery.

To control life-threatening seizures, patient H.M. underwent surgery that removed the hippocampus, amygdala, and part of the association cortex from both temporal lobes. The top panel indicates the position in the brain of the slices shown in (A) and (B). These MRI scans compare a typical control participant (left hand column) with patient H.M. (right hand column).

(from Corkin et al., [1997](#))

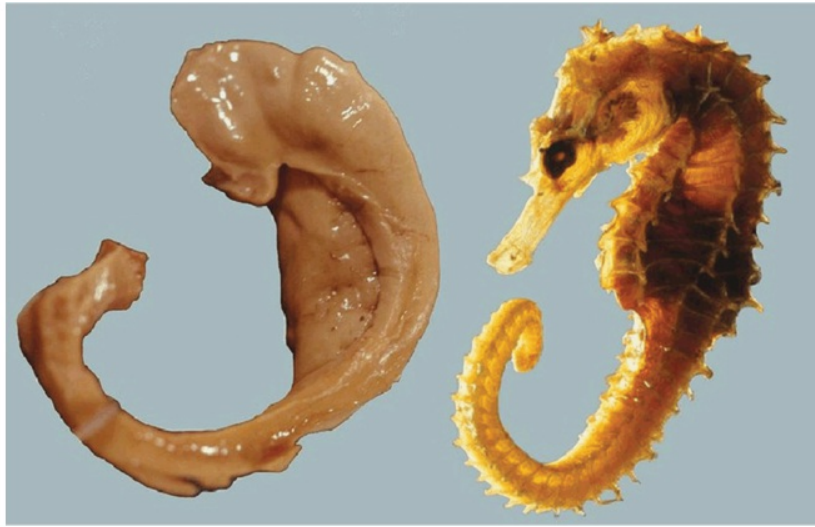


Figure 9.3 The anatomy of the hippocampus.

Anatomical dissection of the hippocampus showing how its shape is similar to that of a seahorse.

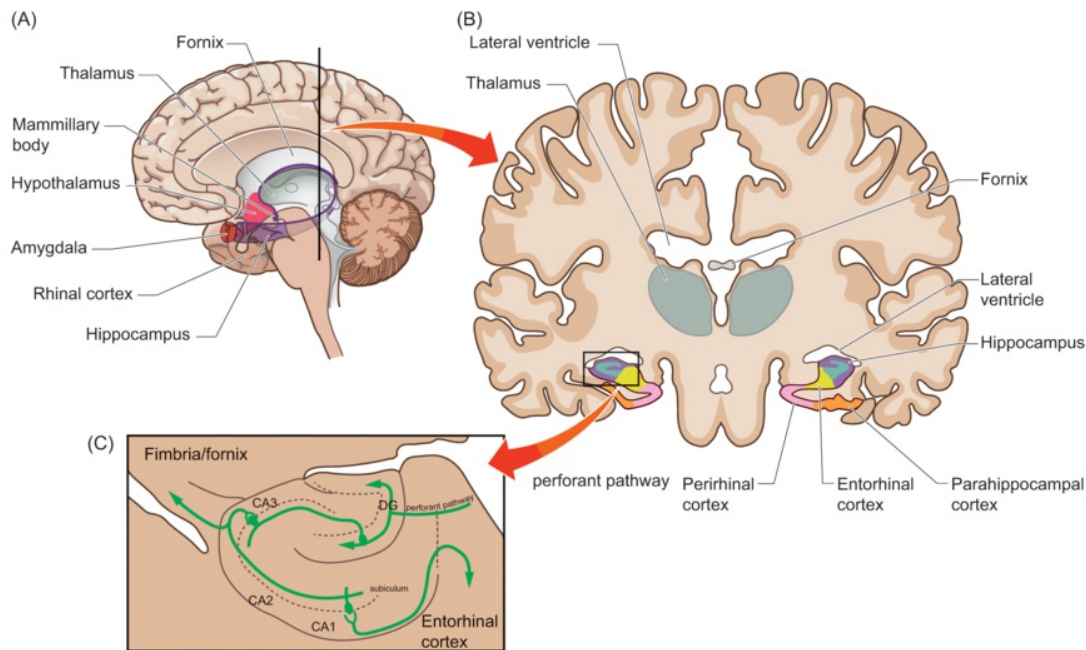


Figure 9.4 The neural circuitry of the hippocampus.

Shown here is the location of the hippocampus in the brain from (A) lateral and (B) coronal perspective. Inset (C): The hippocampus in a cross-sectional view. As shown here, information from a variety of brain regions converges on the dentate gyrus of the hippocampus via input from the perforant pathway from adjacent entorhinal cortex (from Smith et al., [2012](#)). Information then courses through the hippocampus in a mainly unidirectional manner through different hippocampal subfields (e.g., Area CA1, CA2, CA3). With regards to output, there is both a reciprocal loop back out of the hippocampus to the entorhinal cortex via the subiculum and an additional output to the rest of the cortex via the fimbria which turns into the fornix.

In addition, amnesia can also result from damage to the closely related [midline diencephalic region](#), involving particularly the dorsomedial nucleus of the thalamus and the [mammillary bodies](#) of the hypothalamus. Damage to these regions can originate in a number of ways – for example, as occurs in Korsakoff’s disease, following chronic alcohol abuse, or sometimes through an accident as shown in [Figure 9.5](#). Regardless of etiology of hippocampal or other brain damage, the fundamental nature of the deficit is an inability to form most new long-term memories.

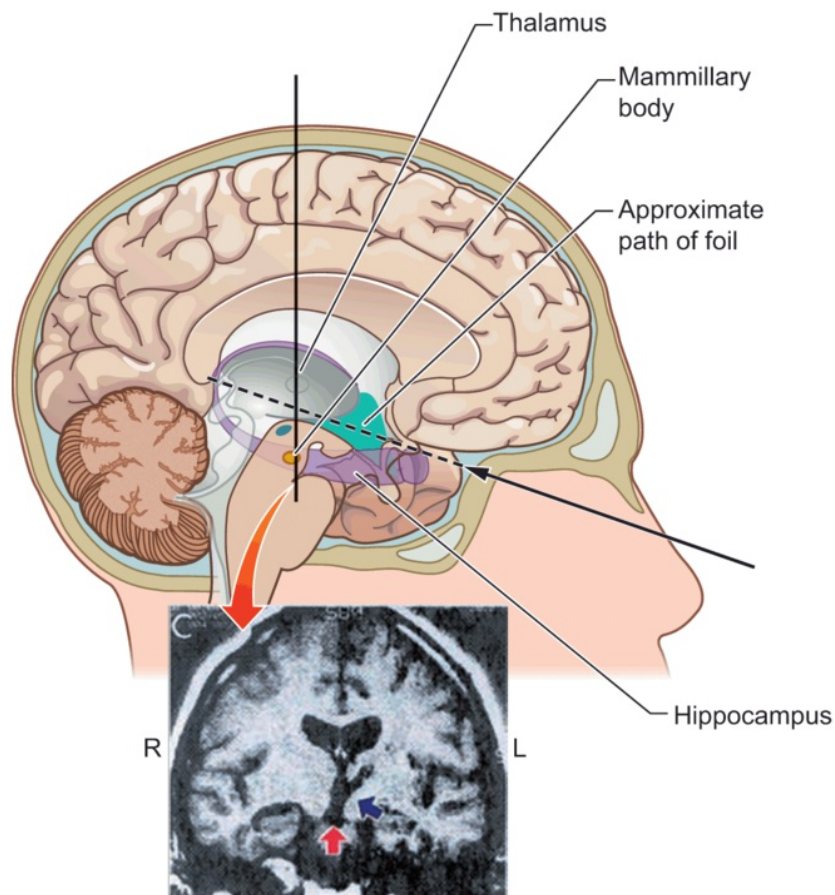


Figure 9.5 Damage to the midline diencephalic structures can also lead to amnesia.

(Above) Shown here is the location of the mammillary bodies, one on each side of the brain's midline, relative to the thalamus. Damage to these regions occurs in Korsakoff's amnesia, but can also occur via accident. In the case of patient N.A., damage to these midline structures occurred via a fencing foil, the path of which is shown by the black arrow (from Squire, 2011). (Below) An MRI scan of N.A.'s brain. The red and purple arrows indicate areas damaged by the foil. The mammillary bodies are no longer visible, as they were obliterated by the accident.

(from Squire, 2011)

Global Nature of the Deficit

One of the most fundamental aspects of amnesia resulting from hippocampal damage is that it is global with regard to modality and material. For example, H.M.'s impairment was shown to affect memory of material presented in the visual, auditory, somesthetic,

and even olfactory modalities (see Corkin, [1984](#); Milner et al., [1968](#)). The deficit in amnesia also applies to many different kinds of material, affecting memory of both verbal and nonverbal material, spatial and nonspatial information, meaningful and nonsense stimuli, and so forth.

The modality- and material-general of hippocampal amnesia has been crucial in identifying the disorder as specifically one of memory functions rather than perceptual, linguistic, or other cognitive processing functions. Damage to the cortical brain systems critical for processing language, visual objects, or motor sequences can cause memory problems, but these are invariably modality- and/or material-specific. For example, in visual agnosia the patient fails to identify objects presented visually, but has no problem identifying the same objects by touch or sound (see [Chapter 6](#)). Unilateral damage to the [hippocampal system](#) can produce [material-specific memory disorders](#). After left-hemisphere damage, memory is selectively impaired for verbal material, whereas after right-hemisphere damage, memory is impaired for nonverbal materials (e.g., Milner, 1971; see Chapter 2, page [43](#)). When there is bilateral damage, as in the case of H.M., a general impairment across all types of materials occurs.

This modality- and material-general aspect of memory can be observed regardless of how memory is assessed. Consider a paradigm in which an amnesic hears a list of 15 words to remember (e.g., motel, cathedral, broker, bowl, cyclone ...), and then is tested 30 minutes later. Memory deficits are observed regardless of whether the amnesic uses [free recall](#) (the patient is told, “Report all of the words on the study list”), [cued recall](#) (the patient is told, “Report all the words from the study list that were examples of buildings or that began with the letter ‘b’”), or [recognition memory](#) (the patient is given 15 word pairs, each containing one item from the list and one novel item, and for each pair is asked, “Which of these two words [‘cabin’ or ‘cathedral’] was on the study list?”). Any theory of memory must take into account the global nature of the deficit observed after damage to the hippocampus.

Temporal Profile of Affected Memories

Memory impairment observed in amnesia can be divided into two distinct temporal phases: anterograde and retrograde amnesia. So far we have emphasized [anterograde amnesia](#), which is the deficit in learning new information after the onset of amnesia. Yet, anterograde amnesia virtually always occurs in association with at least some retrograde amnesia. [Retrograde amnesia](#) is the impairment in memory for information that was acquired prior to the event that caused the amnesia – a deficit stretching back in time to some point before the onset of amnesia (see [Figure 9.6](#); see Kapur, [1999](#), for a longer discussion). The temporal extent of retrograde amnesia can vary greatly across individuals, from minutes to decades (e.g., Kapur and Brooks, [1999](#); Bayley et al., [2006](#)).

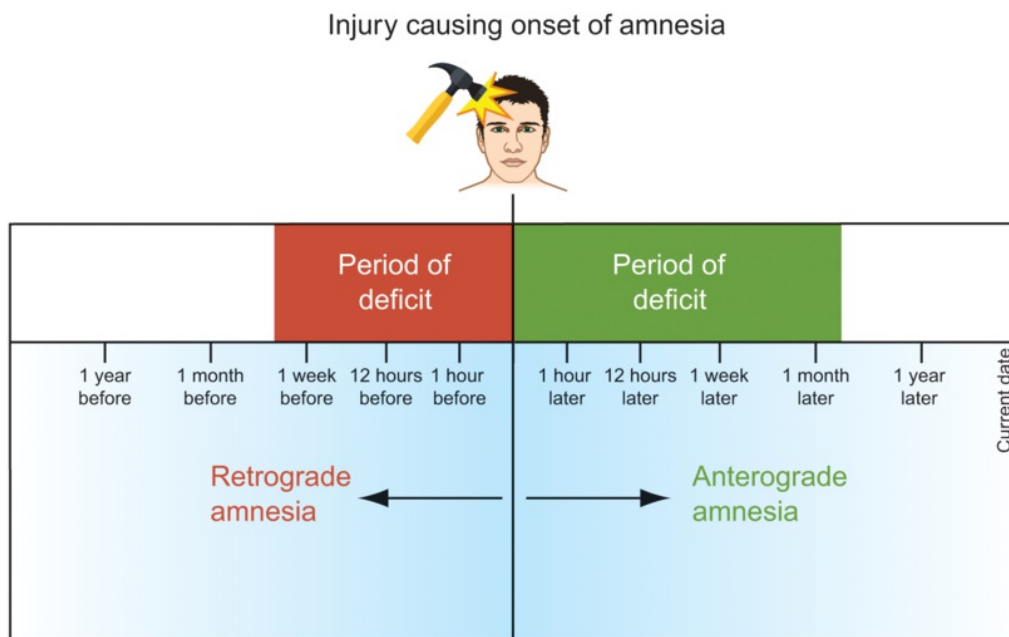


Figure 9.6 Timeline illustrating anterograde and retrograde components of amnesia.

Any memory deficit that extends forward in time from the onset of amnesia and prevents the formation of new, enduring memories is known as anterograde amnesia. Any memory deficit that stretches backward in time from the onset of amnesia and prevents retrieval of information acquired prior to the onset of the amnesia is known as retrograde amnesia.

Many instances of retrograde amnesia are temporally limited, meaning that they are only observed for a specific period of time. In some cases, the duration of the retrograde amnesia is brief. For example, in mild closed head injury (associated with car accidents, falls, and sports-related activities), the retrograde amnesia extends back less than 60 minutes before the injury in about 95% of patients (Paniak et al., [1998](#)). In other cases, it can extend to years, as in amnesia associated with bilateral electroconvulsive treatment (ECT) (Fraser et al., [2008](#)). For example, in a clever experimental design, researchers asked patients about television programs that had aired for just one season (in this manner the researchers could be assured that the memory for the show had to be acquired at a particular point in time, and not years later, for example, by viewing reruns). Patients who had received ECT were disproportionately impaired in recalling information about shows aired one to two years prior to the ECT treatment, and often could not even remember the single most salient fact about such a show, including whether it was a comedy or a detective show. However, they could remember much more, including even specific episodes, about shows that aired further back in time (Squire and Cohen, [1979](#)) (see [Figure 9.7](#)).

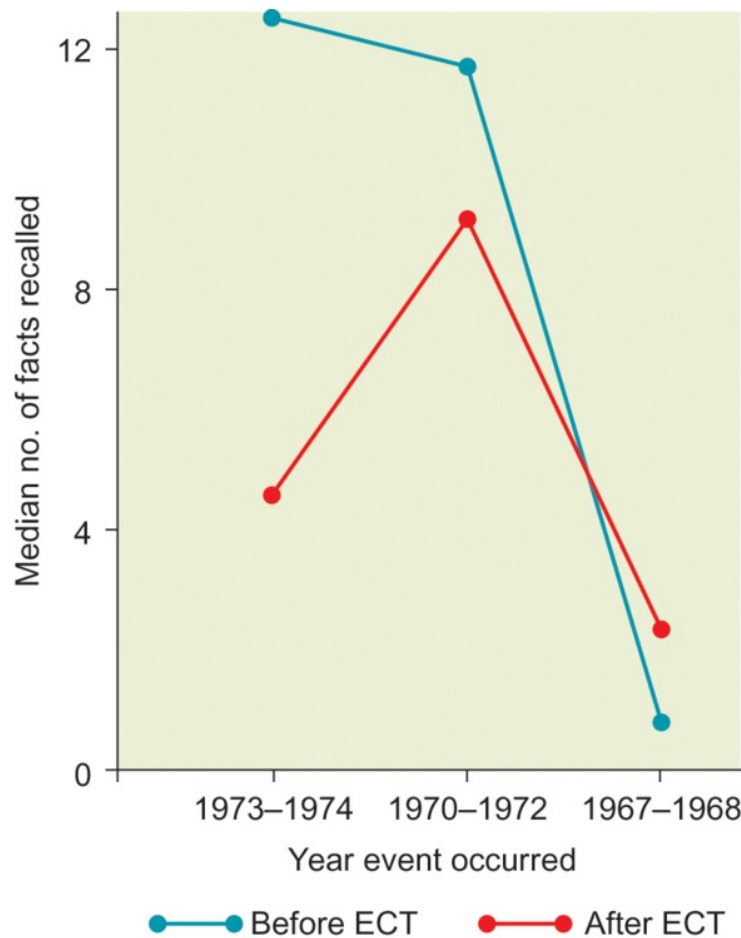


Figure 9.7 Evidence of temporally limited retrograde amnesia in patients who have undergone electroconvulsive treatment.

In the 1970s, 20 individuals were asked to recall information about former television programs that aired for just one season before and after a series of ECT treatments. Shown here is a graph of the median number of facts recalled. Before ECT (blue line), patients showed a normal forgetting curve; their best recall was for shows from the most recent time period, and their poorest recall was for shows from the most remote time period. After ECT (red line), a selective impairment occurred in the recall of shows from the most recent time period.

However, in other cases, the retrograde amnesia covers an extensive period of time, going back decades in patients with progressive disorders like Korsakoff's, Alzheimer's, Parkinson's, or Huntington's disease (e.g., Reed and Squire, [1998](#); Kopelman et al., [2009](#)). For example, when asked to name the current US president, these patients are likely to name someone whose presidency occurred during the

patient's youth, such as Harry Truman or Dwight Eisenhower (whose terms ran from the mid-1940s through the late 1950s). Scientists have suggested that the greater the damage to hippocampal regions, the greater length of retrograde amnesia and that the most extensive retrograde amnesias may be associated with damage that extends beyond medial temporal regions into lateral regions (Bright et al., [2006](#)).

Typically, retrograde amnesia is characterized by a [temporal gradient](#) in which there is a greater compromise of more recent memories than more remote memories. This effect is often referred to as [Ribot's Law](#), after the nineteenth-century scientist, Théodule Ribot, who first noted it (Ribot, [1881/1882](#)). Gradients of retrograde amnesia suggest that memory might undergo change during the time after learning. Researchers have interpreted this temporal gradient as suggesting that memories undergo a process of consolidation or strengthening with time. Memories closest to the event that caused amnesia are most affected because the insult to the brain precludes the memory from being consolidated. Those memories further away from the event have already undergone at least some consolidation, and are therefore not as adversely affected. The temporal gradient has been observed in patients in whom the retrograde amnesia extends back decades, such as patients with Korsakoff's disease and Alzheimer's disease (Kopelman et al., [1999](#); Meeter et al., [2006](#); Sadek et al., [2004](#)). In one study, patients were asked to identify the faces of public figures who were famous across many decades (Albert et al., [1979](#)). Patients were more likely to correctly identify them in older photographs (such as Ronald Reagan as the 1930s- to 1950s-era actor) than in more recent photographs (Ronald Reagan as the 1970s- to 1980s-era American politician and president) (see [Figure 9.8](#)). In part, such a temporal gradient may exist in these individuals because the onset of the disorder is somewhat gradual. As such, they may not have been acquiring memories normally for an extended period of time, contributing to the gradient.

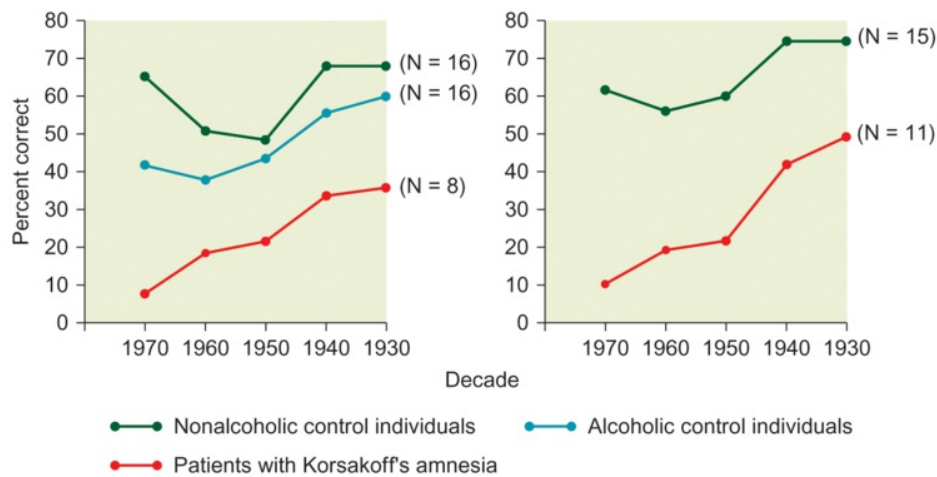


Figure 9.8 Evidence of extensive retrograde amnesia in patients with Korsakoff's disease.

Alcoholic and nonalcoholic control individuals and patients with Korsakoff's disease were asked to identify photographs of public figures who became prominent during different decades from the 1930s through the 1970s. Across all decades, the performance of patients with Korsakoff's disease was impaired compared with that of the control individuals. (Left) Results of research by Cohen and Squire (1980). (Right) Results of research by Albert, Butters, and Levin (1979).

Not all forms of amnesia exhibit a temporal gradient, however. Instead, some are relatively uniform across time periods. Such "flat" gradients have been observed in people with focal damage to midline diencephalic structures, and Huntington's disease (Kopelman et al., 1999; Sadek et al., 2004) (see Chapter 16), as well as in some etiologies of amnesia with hippocampal system damage (e.g., Mayes et al., 1994; Noulhaine et al., 2007). The existence of these "flat" gradients is inconsistent with many theories of the neural underpinnings of memory that we discuss in more detail later in the chapter when we discuss consolidation. As a result, researchers are continuing to determine whether such flat gradients are restricted to certain types of patients and certain types of memory (see Kopelman and Bright, 2012, for discussion).

Notably, even when retrograde amnesia is observed, it typically is limited to memories for particular events or episodes of the past. This type of memory is called [episodic memory](#) and refers to those autobiographical memories that are specific to our

own unique experience that includes context about the time, space, and circumstances under which a particular experience occurred. As long as the damage is limited to the hippocampal system and does not extensively involve neocortical brain regions, patients will have intact memory for the basic perceptual, motor, linguistic, and intellectual competences they had before the onset of amnesia. They also retain information learned early in life about language, objects, and the world in general (Cipolotti and Bird, [2006](#)). This dissociation – between the ability to retain information in general and the inability to remember specific life events – is an important attribute of amnesia and plays a central role in theories of the neural underpinnings of memory, a point we will revisit later.

Spared Abilities

Notably, while amnesic patients display a deficit of long-term memory, which is the ability to retain information for as long as a lifetime, other aspects of memory are spared. In this section, we will examine the types of memory that are preserved in amnesic patients. The fact that these abilities are spared after hippocampal damage implies that other somewhat independent memory systems must exist in the brain, an issue we consider in greater detail later in the chapter in the section on multiple memory systems.

Spared Working Memory

In contrast to long-term memory, working memory is unaffected. Working memory is the ability to hold a limited amount of information on-line over the short term while the information is being actively used or processed. In common parlance, you might think of working memory as the mental equivalent of a cross between Twitter and Snapchat. Like Twitter (restricted to 280 characters), working memory is limited in its capacity, in this case to approximately seven items. Like Snapchat, which disappears after 10 seconds, information is only held in working memory for a relatively short amount of time, on the order of seconds to minutes.

A classic experiment illustrates the dissociation between long-term and working memory. In this experiment, a [digit span task](#), in which the person has to report back a sequence of items, such as digits, read one at a time by the experimenter. H.M.'s performance was within the normal range (7 \pm 2 items), indicating an intact working memory span. However, once his working memory span was exceeded, his performance suffered. This deficit was demonstrated by an [extended digit span](#) task, in which the same digit string is presented on each trial but with an additional digit added to extend the span. For example, participants are repeatedly given a string of digits that surpasses their digit span by one digit (e.g., 2-7-9-1-3-4-8-6) until it can be correctly recalled. Then they are given multiple trials with the same initial string but with an additional digit at the end (e.g., 2-7-9-1-3-4-8-6-5) until it can be recalled, and so forth. Neurologically intact subjects can recall strings of at least 20 digits using this procedure, because they use long-term storage in addition to working memory to complete the task. H.M. could not recall even a single string that was one digit larger than his span, despite 25 repetitions of the same string. In other words, he was unable to use long-term memory to extend the list of digits beyond his working memory span (Drachman and Arbit, [1966](#)).

Because patients with amnesia have intact working memory, they perform normally when the delay between the exposure to information and the memory test is short, or when the amount of material to be remembered is small. Thus, they can comprehend episodes and events normally if those events unfold over a relatively short time, and they can engage in reasonable discourse if the conversation remains on topic. However, because their memory impairment emerges with longer delays, they are unable to retain this information for the long term. Consequently, these individuals exhibit little cumulative learning across events or episodes. For example, you can comprehend this paragraph and then integrate it not only with the knowledge acquired from the previous paragraphs in this chapter, but also with information from the preceding chapters. Patients with amnesia, such as H.M., cannot do this. Indeed, patients with the most

severe amnesias often comment on the difficulty that reading presents to them. As a result, they have great difficulty learning new facts and data about themselves or about the world.

When amnesics do show evidence of such learning, it is usually strongly tied to information they acquired prior to the amnesia that is highly salient to them and likely relies on regions outside the hippocampus. For example, capitalizing on H.M.'s love of crossword puzzles, scientists were able to show that he could learn some new information. At the time that H.M. grew up one of the most devastating diseases was polio, a virus that mainly affected children and left them with lifelong muscle weakness and deformities. It was not until the mid-1950s (after H.M.'s surgery in 1953) that a vaccine was created by Jonas Salk that put the world on the current-day path to the almost total eradication of the disease. H.M. was able to learn about the Salk vaccine in the course of doing crossword puzzles most likely because it was tied to clues about polio, which he knew about prior to his surgery and was salient to him (Skotko et al., [2004](#)).

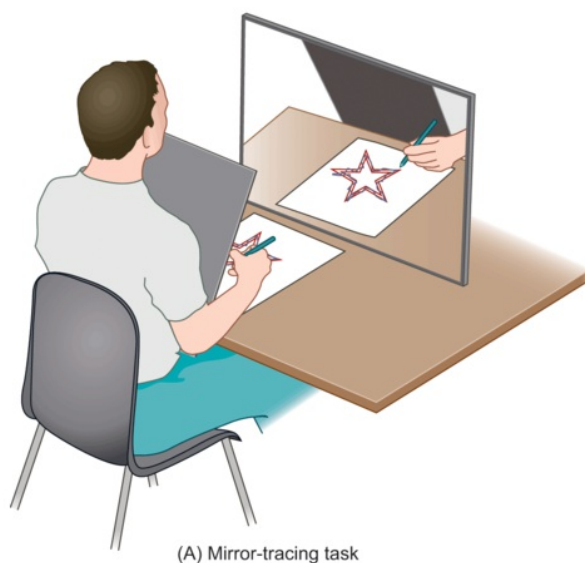
The dissociation between a deficit in long-term memory and fully functional working memory is also seen in nonhuman primates with hippocampal damage. This effect is demonstrated in a variant of the [delayed nonmatch-to-sample task](#) (e.g., Gaffan, [1974](#); Mishkin and Delacour, [1975](#)). On each trial in this task, an animal is exposed to one of a large set of objects. Following a delay, the object just viewed is presented again, this time together with another from the set of available objects. To receive a reward, the animal must select the object that was not previously presented (i.e., the nonmatch object). Following extensive hippocampal system damage, performance is markedly impaired for delays longer than about 10 seconds, but normal for shorter delays (Mishkin, [1982](#); Zola-Morgan and Squire, [1985](#)). This dissociation between intact short-term memory abilities and disrupted long-term memory abilities points to the fact that these two types of memory processes rely on different neural structures.

Spared Skill Learning

In the course of the extensive studies of H.M.'s memory deficit, researchers noticed a funny thing: In spite of his pervasive and profound long-term memory impairment he nonetheless appeared to be able to learn on some tasks! Furthermore, even though H.M. was getting better and better at these tasks, he seemed to be totally unaware that he was learning anything. Rather, he would just comment "Huh, this is easier than I thought it would be."

What researchers discovered was that H.M. and other amnesics show evidence of spared learning but only on certain kinds of tasks. In general, these tasks involve appreciating regularities in the environment that allow for increasingly improved performance. One main category of preserved learning is [skill learning](#), which refers to the acquisition – usually gradually and incrementally through repetition – of motor, perceptual, or cognitive operations or procedures that aid performance.

One of the first examples of skill learning that scientists observed in H.M. was on a [mirror-tracing task](#), which involved tracing the outline of a figure (such as a star) by looking in a mirror (Milner, [1962](#); Corkin, [1968](#)) (see [Figure 9.9](#)). Across sessions, the number of times H.M.'s drawing fell outside the outline of the figure decreased, as did the time it took him to complete the task. Similar learning is demonstrated by amnesics on other perceptual-motor skills such as [rotary pursuit](#), in which the person has to track a circularly moving target (e.g., Brooks and Baddeley, [1976](#); Cermak et al., [1973](#)).



(A) Mirror-tracing task

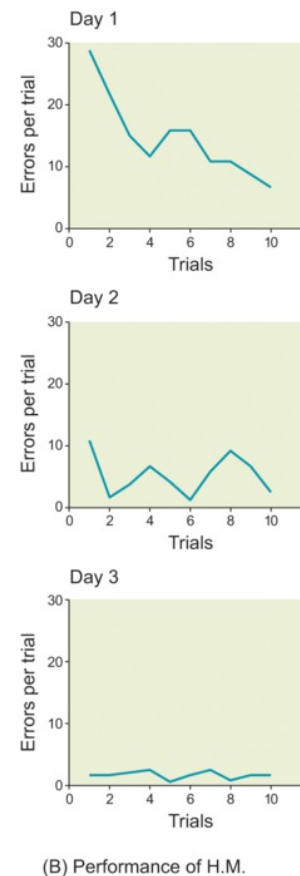


Figure 9.9 The mirror-tracing task, which first provided evidence for new learning in the amnesic, H.M.

(A) In this task, one must trace between the lines of a star while looking in the mirror. (B) As shown here, the number of errors (going outside of the lines) exhibited by H.M. decreased with practice. His performance improved at about the same rate as observed in typical control participants.

Notice that in these tasks, the person is doing exactly the same task over and over again. Researchers wondered whether amnesics were learning the specific instances of these tasks (e.g., mirror drawing of a star, compared to mirror drawing of an octagon) or a skill in general (e.g, mirror drawing in general). To examine this question, they used a [mirror-reading task](#) (Cohen and Squire, [1980](#)). For this task, word triplets are presented in mirror-image orientation, and the viewer reads them aloud as quickly and accurately as possible (see [Figure 9.10A](#)). Of critical importance, half of the word triplets are presented multiple times, appearing once in each block of trials ([Figure](#)

[9.10B](#)), and half are presented only once during the experiment (right-hand panel of [Figure 9.10C](#)). With practice, neurologically intact participants show improvements in reading both the mirror-imaged words they have seen before and the new mirror-imaged words. In this way, they acquire the skill of reading any word presented in mirror-imaged text ([Figure 9.10C](#)), not just specific instances of mirror-reversed words. Like neurologically intact people, amnesic patients show improvements on both the practiced and new mirror-imaged words.

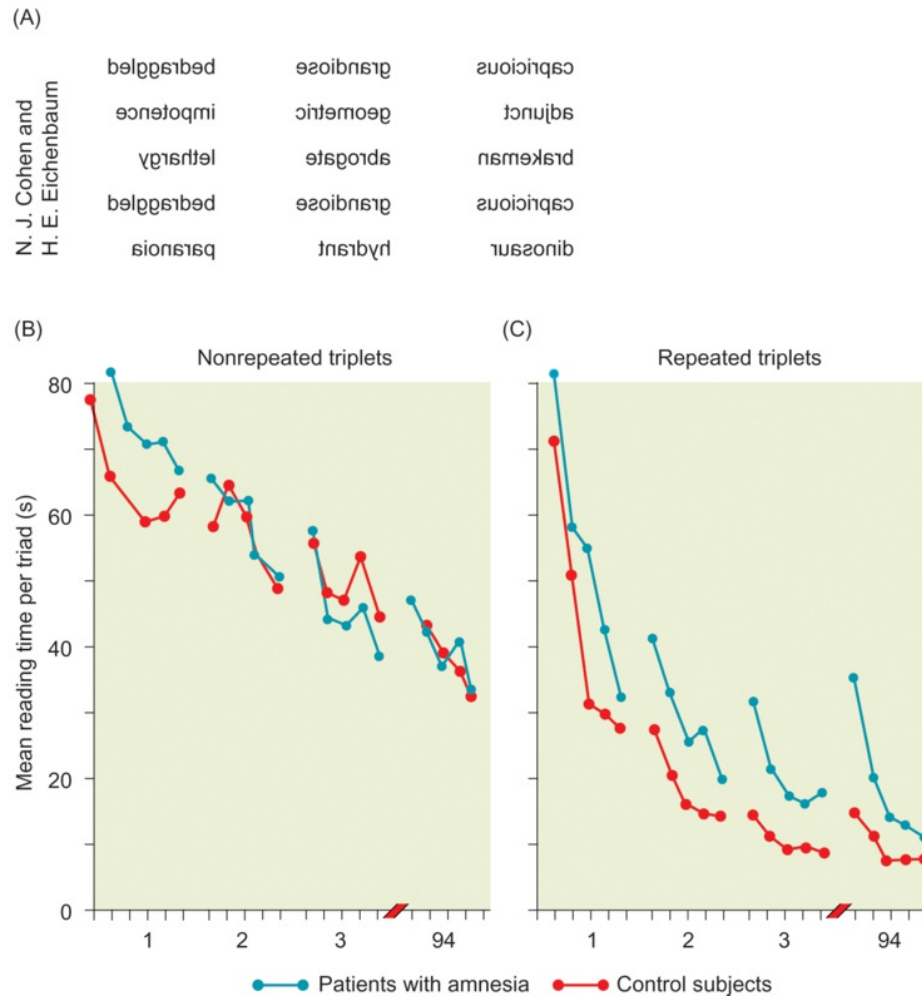


Figure 9.10 Example of spared perceptual skill in patients with amnesia.

(A) Examples of the mirror-image word triads used in a mirror-image reading task.

(B) Just like control individuals, patients who have amnesia increased the speed with which they could read the triads. This increase in all these patients occurred not only for repeated triplets (triplets that they had seen before; graphs on the right), but also for (C) new (nonrepeated) triads (graphs on the left). The increase in the reading times for novel triplets indicates that the patients with amnesia were learning the perceptual skill of mirror-image reading.

What is even more remarkable is that this spared learning occurs even when the patients cannot recollect the training events during which the new skills were acquired, cannot recall or recognize the material on which the increasing skill is demonstrated, and have no insight into their improved performance! This dissociation in amnesia is probably best illustrated by the [word-stem completion task](#) (Graf et al., 1984). In this

task, people are given a list of words to study. After a delay, memory for the words is then tested in two ways, both of which involve the presentation of three-letter stems (e.g., mot, cyc). In one condition, the cued-recall condition, participants are asked to recall the word from the study list that started with those same three letters. Not surprisingly, patients with amnesia perform poorly in this condition compared with neurologically intact control participants. In the other condition, the word-stem completion condition, participants are to report “the first word that comes to mind” that completes each stem. If the participant is influenced by prior exposure to the word list then he or she should complete the stem with a word from the study list, like motel and cyclone, more often than a word not on the list with the same initial three letters, such as mother or cycle. Patients with amnesia are just as biased to complete the stems with items from the study list as are neurologically intact adults (see [Figure 9.11](#)). Thus, while amnesics have no recollection of the items, exposure to the items nonetheless influences their behavior.

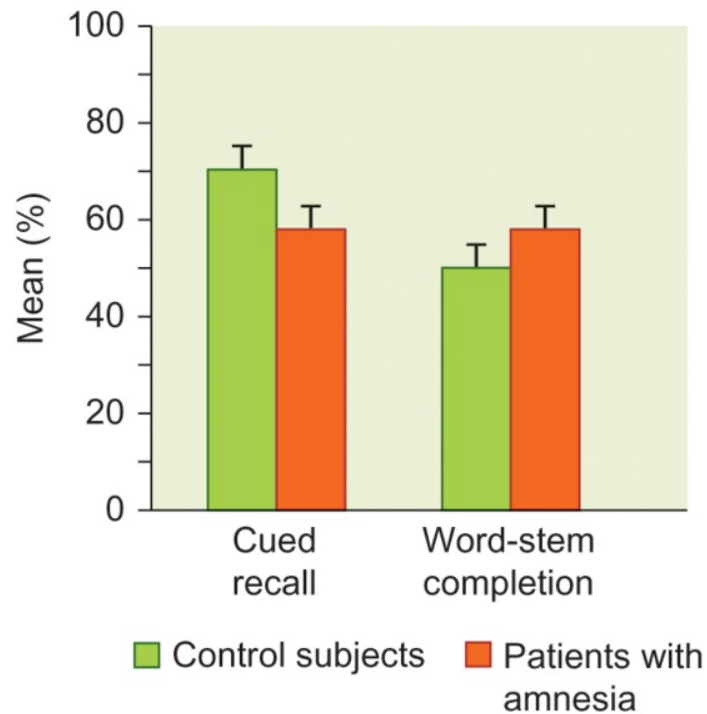


Figure 9.11 Evidence of a dissociation between disrupted cued-recall and intact word-stem completion in patients with amnesia.

Patients with amnesia are impaired relative to control individuals on cued recall of words from a previously studied list (left). However, when asked to complete the word stems with the “first word that comes to mind,” these patients are just as biased as neurologically intact control people to report the word that they saw previously on the list (right). In other words, the prior exposure primes their behavior even though they cannot explicitly recall their experience.

This dissociation between episodic memory and other forms of memory has also been demonstrated in research with both rodents and nonhuman primates. In probably the most classic example, rats with damage to the hippocampal system exhibit marked deficits in learning and remembering spatial relations, such as required in the [Morris water maze](#) (Morris, [1981](#)) (see [Figure 9.12A](#)). In this task, the rat is placed in a circular tank filled with an opaque liquid that obscures a slightly submerged platform. The platform is positioned at a constant location relative to various visual cues outside the maze (i.e., objects placed around the room, such as light fixtures, doors, and windows). From trial to trial, the animals are placed into the tank at different locations

around the circumference of the pool. Across trials, normal animals learn the position of the platform in relation to the extra-maze cues, and thus the time it takes them to swim to the platform decreases rapidly (see [Figure 9.12B](#)). In contrast, a rat with hippocampal system damage does not learn the relations among the cues (see [Figure 9.12C](#)) and must search exhaustively each time for the platform's location, not reaching it any quicker from trial to trial (e.g., Sutherland et al., [1983](#)). However, if the platform is always in the same place relative to the start position, animals with hippocampal damage show no impairment (Eichenbaum et al., [1990](#)). This spared ability is similar to what we observed in humans with hippocampal damage; they retain the ability to perform a well-practiced task in which the performance requirements do not change from episode to episode.

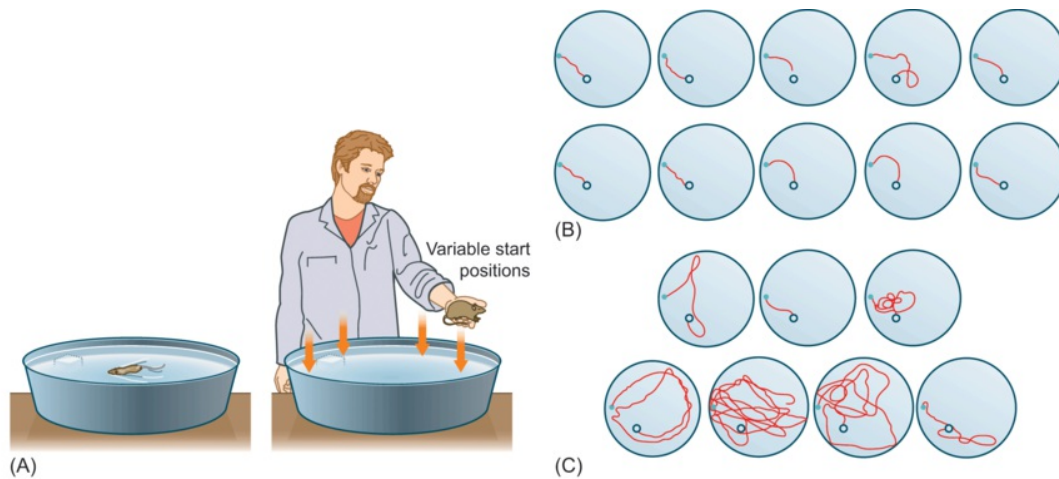


Figure 9.12 Morris water maze task used in animal models of amnesia.

(A) The rats are placed in a circular pool near the perimeter. Submerged in the pool is a platform on which the animal can rest, but which is hidden from view because the liquid in the pool is opaque. The position of this platform is constant relative to various objects around the room, but the animal is placed into the pool at various start locations across the different training trials. Good performance on the task requires the animal to learn to associate the spatial relations between different landmarks and the platform. (B) The path (red line) from a specific starting point to the escape platform for each of 10 normal rats who had only sham lesions. Over a series of trials, normal animals can learn the location of the escape platform, which permits them to swim short, direct paths to the platforms. (C) The paths for seven animals with hippocampal-system damage. Because these animals fail to learn the location of the escape platform, they spend much time swimming around the pool.

So what have we learned about memory from amnesia? First, we have learned that medial temporal lobe structures appear to be critically important for the formation of new long-term memories. Second, it is clear that the neural systems for long-term memories are in part separable from those for short-term memories. Third, the dissociation between skill learning and recognition memory suggests that these two types of memory may rely on different systems. We next examine what type of processing may best characterize these distinct learning systems.

Multiple Memory and Learning Systems

The striking dissociation between memory abilities that are impaired versus spared in amnesia has led to the view that there are multiple long-term memory systems. As the evidence from amnesia suggests, one of these memory systems is thought to rely on the hippocampal system, whereas at least one other memory system does not. Although researchers agree on this point, they do not agree on exactly how best to describe the differences between such systems. Next we will try to provide a general overview of some of the contrasts that have been proposed.

What Distinguishes Memory Systems?

One influential theory proposes a dichotomy between explicit and implicit memory. The memory system that is lost in amnesia has been called the [explicit memory system](#), because it permits the conscious recollection of prior experiences and facts. Another system, the [implicit memory system](#), allows prior experience to affect behavior without the individual consciously retrieving the memory or even being aware of it (e.g., Schacter, [1987](#)). Because amnesic patients cannot consciously engage in introspection about the contents of their knowledge, they are said to have “memory without awareness” (Jacoby, [1984](#)). Rarely, if ever, are neurologically intact people so devoid of familiarity with their previous exposure, while nonetheless exhibiting memory for it. Therefore, some researchers see memory without awareness as a key aspect of amnesia.

Another viewpoint suggests a contrast between declarative and procedural memory. The memory system supported by the hippocampus is referred to as the [declarative memory system](#), because people “know” particular information, and that information can be used flexibly and is not linked to the situation in which it was acquired (e.g., Cohen and Squire, [1980](#)). For example, you can “declare” that the capital of Italy is Rome in situations other than that in which you first learned that fact. Furthermore, you can link that knowledge with other facts about Rome, such as that it is referred to as “the eternal city.” Being asked to provide information about what one did on a particular

date or in a particular class are also examples of explicit/declarative memory. Much of the regular social interaction we have with friends and family is of this nature, where, in sharing the details of our lives, we consciously harken back to specific events and recount the things that happened.

The [procedural memory system](#), on the other hand, appears to support memory of “how” things should be done, allowing for the acquisition and expression of skill. Learning in this system is probabilistic, integrating information across events rather than storing each event separately. Typically, this memory is expressed in situations similar to that in which something was learned. One example of this type of memory is your ability to ride a bicycle. This ability is usually expressed in only one context – when you are on a bicycle – and typically people do not really have conscious knowledge of how such abilities are expressed. This system is unaffected in amnesia, and therefore is independent of the hippocampal system.

Finally, other researchers have characterized the hippocampal system as one that supports [relational learning](#), whether conscious or unconscious, to form conjunctions (Eichenbaum and Cohen, [2001](#); O'Reilly and Rudy, [2001](#)). Relational learning occurs in tasks or situations where performance depends on acquiring memory for the relations among items, especially items associated only arbitrarily or accidentally. One example is learning the names connected with particular people's faces or the addresses and telephone numbers that we learn to associate with them. These relations are arbitrary in that people's real names are rarely, if ever, derived from people's appearance (e.g., parents did not name their child Emily because they decided that she looked like an “Emily”); nor are telephone numbers and addresses in any way meaningfully related to people's names or appearance (e.g., the telephone company did not assign you with a particular number because it seemed an especially good match to your particular name or your particular face). Retrieving the name of the person whom you met yesterday and remembering her phone number cannot be accomplished by deriving such information from other knowledge about the person; rather, you must access a memorized

relationship among the name, face, and number so as to conjoin them. This real-world relational memory task is a challenge for anyone, but it is particularly challenging for patients with amnesia. For example, H.M. never learned the face–name pairings of any of the people who saw him and tested him each year (e.g., Corkin, [1984](#)). Thus, this system represents relationships and associations among the constituent elements of a given scene or event, such as the co-occurrences of people, places, and things, along with the spatial, temporal, and interactional relations among them, that constitute the event. It also represents relationships among various events, providing the larger record of one's experience over time.

Converging evidence from human neuroimaging and animal research implies that the brain region damaged in amnesia, the hippocampal system, supports memory for relations and associations between items. These associations may be between two items, an item and its context, or the temporal relationship between items (i.e., their sequence) (see Eichenbaum, [2017](#), for review). When tasks place a high demand on memory for the relations among items, disproportionate activation of the hippocampal system is observed. One such demonstration comes from an fMRI study in which the greater the number of associations remembered, the greater the activation in the hippocampus (Staresina and Davachi, [2008](#)). During encoding, people saw items and had to make a decision about the color of each item (e.g., “Is the shade of blue in which a shirt is shown pleasing?” “Is red a plausible color for an elephant?”). After scanning, participants were surprised with a memory task. They were asked a number of questions about each item – “Had they seen the item before?” “What color was it?” “What type of decision did they make about it (i.e., appealing; plausible)?” When participants remember all three attributes (i.e., remembered that they had seen the item, its color, and the decision they made about that item), there was more hippocampal activity than if they remembered just two attributes (e.g., just the item and its color, but not the task; just the item and the task, but not the color), or than if they remembered just the item and nothing else. Notice that increased hippocampal activity is associated with increased

binding together of specific attributes of a particular episode, not that shirts in general can be blue or that elephants are not red.

What is it about the hippocampus that allows it to serve as such a good mechanism for making associations, binding together disparate pieces of information together to be stored in memory? From an anatomical perspective, the hippocampal system receives inputs from the diverse cortical brain regions that perform different mental operations, such as object recognition and spatial processes, and from regions that process information of different modalities, such as vision and audition. This information converges onto the hippocampus via the perforant pathway (refer back to [Figure 9.4](#)). The hippocampus thereby receives highly pre-processed input about the “items” encountered in the environment. Accordingly, it is in a position to receive, and bind together or associate, diverse sources of information, including that about the objects present in the environment, the spatial relations among them, the events in which they play roles, the temporal relations among those events, and the affective and behavioral responses they elicit.

Furthermore, electrical recordings in animal tissue indicate that the hippocampal system also has a neuronal mechanism that allows processing of the conjunctions or co-occurrences of inputs. It exhibits a phenomenon called [long-term potentiation \(LTP\)](#), in which brief, patterned activation of particular pathways produces a stable increase in synaptic efficacy lasting for hours to weeks (see Raymond, [2007](#), for a review). LTP is mediated by a class of neurotransmitter receptors (N-methyl-D-aspartate [NMDA] receptors) that constitute superb conjunction detectors, being activated specifically by converging inputs arriving in close temporal contiguity (e.g., Wigstrom and Gustafsson, [1985](#); Morris, [2013](#)). N-methyl-D-aspartic acid (NMDA) receptors are a type of glutamate receptor, which are excitatory in nature.

Furthermore, the electrophysiological response of hippocampal neurons indicates that they are sensitive to various relationships among significant cues or objects in the environment. For example, as you may remember from Chapter 7 (page [219](#)), when rats are actively exploring the environment, their hippocampal neurons show [place fields](#),

meaning that they fire preferentially when the animal is in a particular “place” in the environment (O’Keefe and Dostrovsky, [1971](#); see Hartley et al., [2014](#), for review). Importantly for purposes of the present discussion, firing of these cells does not depend on any specific environmental stimulus, but rather on the relationships among them. If the relative positions of some of the relevant cues are shifted in some systematic way (e.g., rotated 90 degrees clockwise), the place fields often are correspondingly shifted (e.g., Shapiro et al., [1997](#)). When the environment being explored (e.g., a cylindrical enclosure) is scaled up in size, the place fields may correspondingly scale up (Muller et al., [1987](#)) ([Figure 9.13A](#)). When the boundaries of the environment that is being explored are moved outward, the place fields may be stretched out in size (O’Keefe and Burgess, [1996](#)). Thus, in all cases, the cells are responding not to an exact spatial location, but rather to the relative position between items, meaning that they are sensitive to the relationships between items.

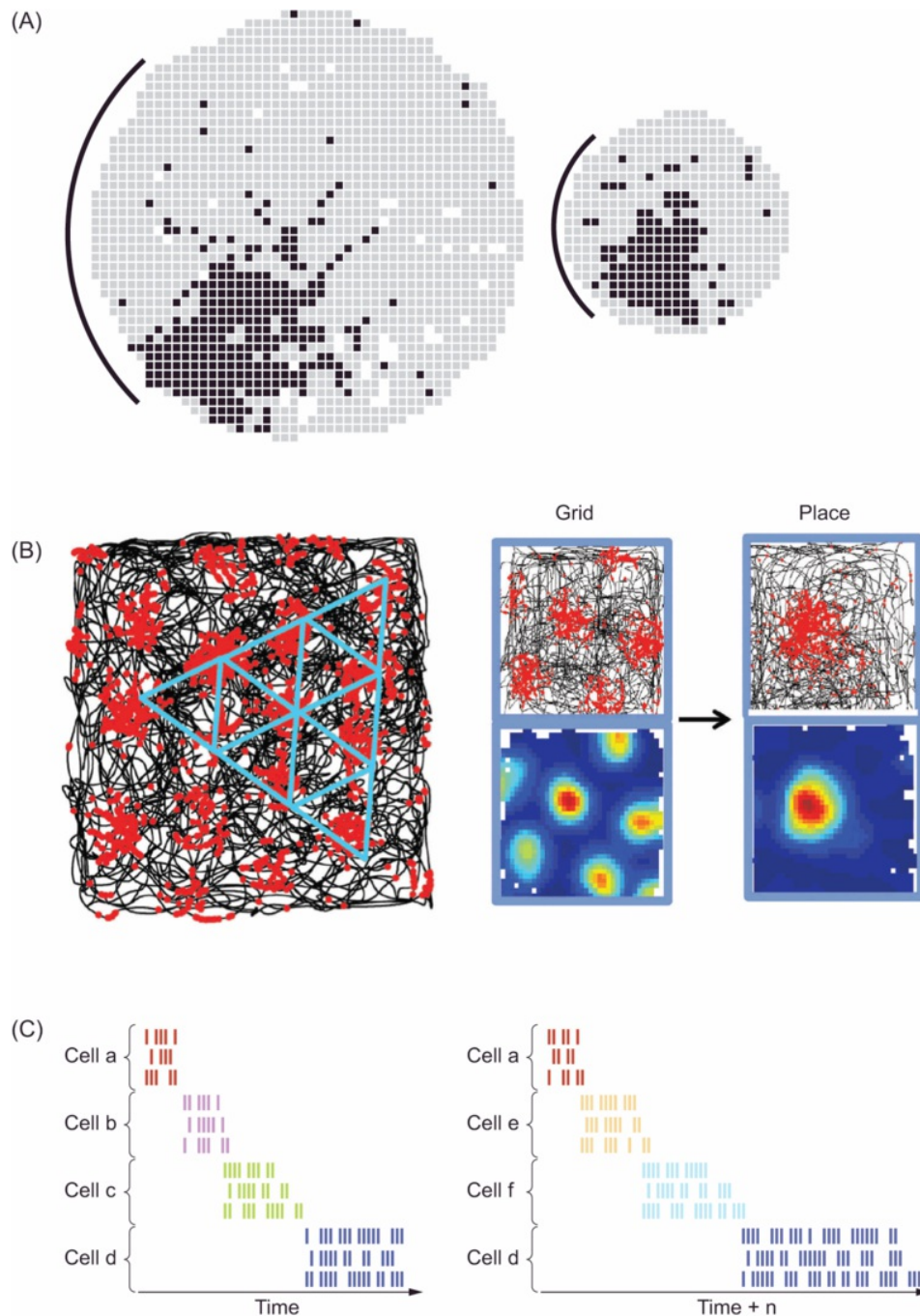


Figure 9.13 Examples of rates and patterns of firing of rat hippocampal neurons.

(A) This figure shows the firing rate of a “place” cell (dark, high; light, low) when a rat was in a given location within an environment. When the animal was placed within a small circular environment (right), the cell fired preferentially to a location within that environment. When the animal explored the larger circular environment (left), the neuron’s place field was “scaled up”: The neuron still fired preferentially

to the same quadrant of space even though that quadrant now encompassed more total area.

(B) Shown here is the activity of grid cells in comparison to place cells. Grid cells (left) fire whenever the animal reaches certain locations in the environment. They are called grid cells because the places in space that yield activation are aligned along a hexagonal grid. In contrast place cells, (right) only fire when the animal is in a specific locale.

(C) Shown here are idealized firing rates of “time” cells in the hippocampus. A solid line indicates a neuronal spike, and three trials are shown (one line for each cell). Notice that across all three trials, each cell fires at approximately the same point in time. (Left) Different cells fire to specific epochs of time. (Right) When the timing of a trial is elongated, cells a and d still fire to the same relative position in time (beginning of the trial and end of the trial respectively), while marking of middle time period is remapped to new cells (cells e and f). Notice that for both space and time, hippocampal cells are sensitive to the relative relationships, whether it be space (sizing up or down of the environment) or time (elongating or shortening events).

(from Eichenbaum, [2014](#))

In addition to place cells, the adjacent entorhinal cortex contains [grid cells](#). Compared to place cells that only fire when the animal enters a particular location in space, these cells have firing fields dispersed across the environment (see [Figure 9.13B](#)). The locations that cause the cell to fire are distributed as a hexagonal lattice, hence the name grid cells. They are thought to help code the animal’s position within the larger environmental context (Moser et al., [2015](#)). The Nobel Prize in Medicine or Physiology was awarded in 2014 to John O’Keefe for the discovery of place cells along with May-Britt Moser and Edvard Moser for the discovery of grid cells.

Subsequently “time cells” were discovered in the hippocampus. These cells fire at specific times during a sequence of experience (Manns et al., [2007](#)). For example, if rats are exposed to a sequence of odors (e.g., a lemon scent followed 10 seconds later by nutmeg scent followed 10 seconds later by rose scent), recordings show that a

distinct population of time cells would fire for each “event,” that is, one set of neurons fires when the lemon scent is presented and another when the nutmeg scent is presented. Later on when presented with the smell of lemon, the hippocampal cells that originally fired to the point in time in which the lemon was presented would be followed by activity 10 seconds later by cells that were active during the time period of nutmeg presentation, even though no nutmeg smell was presented. Moreover, just like place cells, the activity of these cells is sensitive to the relative time period between successive events. For example, if the initial event is changed (e.g., elongated in time), the activity of cells sensitive to subsequent events is “scaled” by a similar factor (Eichenbaum, 2014) (see [Figure 9.13C](#)). Time cells can be thought of as complementary to place and grid cells. Whereas place and grid cells provide information on the spatial associations that characterize an event, time cells provide information on the temporal associations. All of these findings suggest that cells in the medial temporal lobe work to flexibly bind together different pieces of information about a particular experience.

Taken altogether, the study of memory, amnesia, and the hippocampal system in humans and animals implicates this brain system as being critical for the formation of certain types of new long-term memories. Scientists continue to debate exactly what are the critical features of long-term memory processing that are supported by the hippocampus, whether it be memories that can be explicitly recollected or those that allow disparate pieces of information to be bound together. Regardless, there is no doubt of the central role that the hippocampus plays in long-term memory.

Memory and Consciousness

As we have discussed above, at least some theories of memory suggest that the hippocampal system supports explicit or conscious memory, while other brain systems support implicit memory or memory for/of which we are not conscious. However, researchers have debated whether conscious recall depends critically on hippocampal activity. Some have argued that the criterion of consciousness is not a useful way to

differentiate between memory systems either from the viewpoint of brain function or computational modeling (Reder et al., [2009](#)).

The hippocampal system does not itself produce conscious awareness, nor is it critical for conscious awareness. Large lesions of the hippocampal region, resulting in profound memory impairments, have no demonstrable effect on consciousness in humans. Furthermore, the degree to which tests require conscious recollection does not seem to be the critical determinant of whether memory performance is impaired or spared in patients with hippocampal damage. When given indirect, implicit tests of memory these patients show deficits as long as the task requires them to learn relations among arbitrarily associated items.

As an example, consider a vocabulary-learning experiment in which H.M. failed to show evidence of learning the definitions of uncommon words, such as *tyro* and *cupidity* (Gabrieli et al., [1988](#)), even when tested with indirect, implicit tests of memory. He was shown a word and then asked to select from a list of choices the definition that “went best” with a word, the synonym that “went best” with it, or the sentence frame it would “best complete.” Notice here that there explicit memory is not required, as he was not asked whether he had remembered having previously seen or had conscious awareness of previous experience with any of the words, yet H.M.’s performance was profoundly impaired.

Importantly, this deficit in relational learning can also be observed in amnesics under conditions in which the specific contextual information – that is, the set of multiple cues that defines a particular episode – cannot be consciously recalled by neurologically intact individuals. For example, in one study, eye movements were recorded after people viewed images of real-world scenes two times each (Ryan et al., [2000](#)). On the third presentation, the participant viewed one of three scenes: a scene identical to the initial presentation (repeated scenes) (see [Figure 9.14A](#)), a scene in which a subtle but important manipulation of the relations among some of the elements of the scene were changed (manipulated scenes) (see [Figure 9.14B](#)), or an entirely new

scene (novel scenes). Eye movements elicited by the different types of scenes revealed two distinct effects in neurologically intact people. One was an effect of repetition: less time was spent sampling locations in previously viewed scenes as compared to novel scenes. Amnesic patients showed this effect, indicating that they are affected by their prior experience with the material, much as is observed with word-stem completion task that we discussed earlier. The second effect observed only in neurologically intact people was a relational manipulation effect, exhibited as increased viewing directed to the regions of change in the manipulated scenes relative to the original scene (see [Figure 9.14C](#)). This effect indicates a sensitivity to the relations among the constituent elements of the originally studied scenes. Amnesics failed to show the relational manipulation effect, thereby revealing a selective deficit in memory for relations among items, even though it was tested implicitly without need for conscious awareness (but see Smith and Squire, [2008](#), for an alternative viewpoint regarding what type of memory is indexed by eye movements).

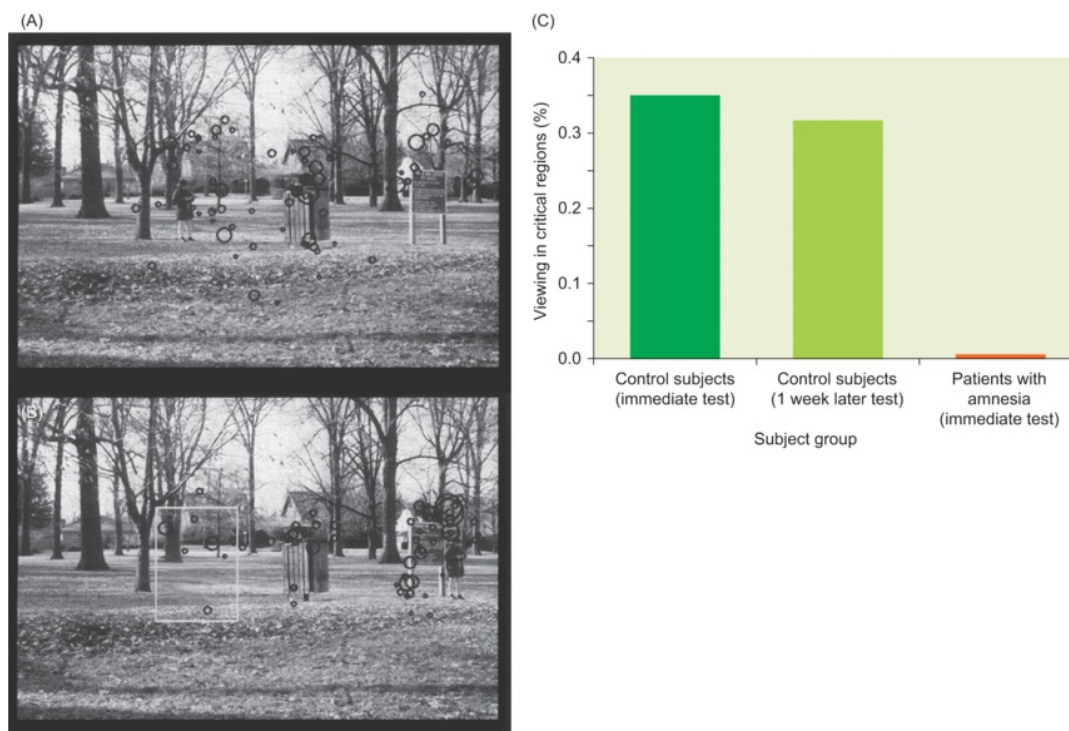


Figure 9.14 Eye-movement monitoring to assess implicit memory.

(A) example of an original scene in a relational manipulation experiment. Participants viewed the scene twice, then saw either the original scene again or (B) a

manipulated version in which relations among the objects in the scene were changed. Superimposed on the scenes in A and B are eye movements made by one of the neurologically intact participants in the study (the circles represent the eye fixations) ([A] and [B] courtesy of Neal J. Cohen). When the participant viewed the original version, most eye movements were directed to the three objects in the center foreground: the person, the wooden trash receptacle, and the sign. When viewing the manipulated scene, the participant looked to the position where the person had been standing, even though it was empty and the person was positioned elsewhere. Hence, eye movements provide an implicit measure of the person's knowledge about the scene.

(C) A graph of data from this experiment. Control individuals tested either immediately after viewing the scenes or one week later exhibited implicit memory for the relations among objects because they spent much time viewing the region of the scene in which the relations had been manipulated. This implicit memory was shown even though they couldn't explicitly remember whether the scene they were currently viewing was the same (or different) from that viewed a week earlier. In contrast, patients with amnesia did not spend time looking at that region, an indication that they lacked the ability to remember relational information even when it was assessed implicitly.

Moreover, assuming that the hippocampus supports "conscious recollection" makes it difficult to address whether or not animal studies yield converging results to those observed in humans. We know that damage to the hippocampal system in rodents and nonhuman primates produces a dissociation among memory capacities that is every bit as compelling as that seen in human amnesia. Such animals show impairments in learning and remembering spatial relations among environmental cues, configurations of multiple perceptually independent cues, contextual or conditional relations, and comparisons among temporally discontinuous events. Yet, the same animals can show normal learning and remembering of a large variety of conditioning, discrimination, and skill tasks, which involve gradual, incremental changes in bias or reactivity to

individual items after repeated exposure. This dissociation parallels closely the dissociation observed in human amnesia.

Nonetheless, the ability to retrieve a declarative memory may indirectly allow for the conscious recollection and conscious awareness of those memories. This idea, however, does not imply that the hippocampus is a structure that is critical or strongly influences consciousness (for a discussion of the neural mechanisms of consciousness see Chapter 10, page [329](#)).

Nonhippocampal Regions Involved in Memory and Learning

The work with amnesics reveals a dissociation between at least two memory systems. So far we have concentrated our discussion on one of those systems, supported by the hippocampus, which allows us to associatively connect information and to retain information about specific episodes in life. Now we turn our attention to the role that other regions of the brain play in memory and learning. As we discussed above, at least some aspects of memory and learning require the incremental accumulation of knowledge across time and practice. This type of memory and learning is supported by specific neocortical regions that are linked to particular domains (e.g., ventral visual processing regions that allow us to learn someone's face) as well as the basal ganglia. Another brain region, the amygdala, plays a special role in supporting those memories that are emotional in nature. Finally, other types of memory require the ability to store knowledge and facts that are not linked to specific episodes in life, such as knowing that Paris is the capital of France. The region of the brain implicated in this type of memory is anterior portions of the temporal pole. In the following sections, we discuss, in turn, each of the neural systems that support such learning.

Domain-Specific Neocortical Regions: Initial Processing and Subsequent Access

Here we discuss evidence that memories are stored, in part, in the same domain-specific brain regions that were originally involved in processing information during a given event or experience. For example, consider areas within the ventral visual processing stream such as inferotemporal cortex (area TE) in the monkey and the fusiform gyrus in humans that support a specific domain of processing, namely, visual object recognition. Anatomical, neurophysiological, neuropsychological, and neuroimaging data all indicate that this region of the brain both processes information about visual objects and acts as the site of long-term storage of memory for those objects. As discussed in [Chapter 6](#), this region is at the end of the “what” visual pathway. Damage to this region results in visual agnosia, which not only prevents individuals from identifying previously known visual objects but also from learning about the visual form of new objects. This association suggests that damage to this region affects both perception and memory of visual objects.

Evidence for a tight coupling of visual processing and visual memories comes from functional neuroimaging studies of neurologically intact humans. The same regions of the visual ventral stream, particularly the fusiform gyrus (e.g., Haxby et al., [1994](#)), become active when an individual reactivates or reimagines a visual form in the absence of the visual stimulus itself. In one study, participants studied words that were paired with either a picture or a sound. At test time, the participants were presented with words individually and had to recall whether they had previously been associated with a visual form or with a sound. When individuals were able to recall the pictures associated with the word, fusiform activation was similar to that observed during initial presentation of the picture (Wheeler et al., [2000](#); for a similar finding, see Nyberg et al., [2000](#)). When recalling the sounds associated with words, activation was observed in auditory regions of the superior temporal gyrus, similar to that observed when the word was initially presented (Wheeler et al., [2000](#)).

In addition, the multi-voxel pattern of activity that is observed when a person is first exposed to a visual object is reinstated when that item is retrieved. For example, in one study people saw a series of famous faces, famous locations, and common objects.

Multi-voxel pattern analysis was used to classify patterns of brain activity that distinguished between the three categories of objects. Later on participants were asked to verbally describe as many of the items as possible. Even before they gave their actual response, the pattern of brain activity predicted which of the three categories of items to which the about-to-be-named item belonged (Polyn et al., [2005](#))! Taken together with the earlier results, we can see that the same regions are activated for the initial processing of perceptual information as well as for its recall, indicating that these neocortical sites are engaged in both processing and memory functions.

Also, neuropsychological disorders that affect particular, circumscribed domains of world knowledge, such as impairment in face recognition or spoken-language comprehension, manifest both as the loss of previously acquired knowledge in that domain and as the inability to acquire new information in that domain. Each such type of knowledge deficit thus seems to reflect damage to the cortical substrate for both the initial processing and memory of that domain of knowledge. However, each of these domains represents only specific elements of memory.

As we experience the world, the various elements that make up a given specific experience are handled by different cortical processors – those involved in vision, audition, language, and spatial processing, to name a few. These same cortical processors also store the outcomes of their processing. Memory for visual elements of the experience is stored in visual processing areas, memory for linguistic elements is stored in language processing areas, and so forth.

Now that we understand that different portions of a given event are processed and stored in separate regions of the cortex, each of which is domain-specific, we are also in a better position to understand how the hippocampus may aid in storing memory for a particular event. The hippocampus has been suggested to be particularly important for binding together information across different cortical areas, rather than for the binding of information within a given brain region (Mayes et al., [2007](#)). Disparate aspects of an experience, such as what your friend said to you, what she looked like, where she was located, and so forth, are bound together as a coherent event or episode because

processing from auditory, visual-spatial, and other regions are tied together by virtue of their interconnections with the hippocampal system. When such information is retrieved, the hippocampus is thought to provide an index that identifies the constituent parts of that memory. This index points to the locations within domain-specific cortical areas so that the various different pieces of a particular event or episode can be reactivated (Tyler and DiScenna, [1986](#)).

So far, we have discussed only situations in which memory for a specific event or episode is to be stored and retrieved. But what if you are learning an association over time within a given domain or incrementally learning a skill? It is generally thought that such experience modifies the organization of domain-specific processors. For example, training monkeys to discriminate among tones of certain frequencies resulted in a larger representational area for those particular frequencies in auditory cortex. In addition, the degree of reorganization within auditory cortex predicted how well the animal could discriminate among frequencies (Recanzone et al., [1993](#)). Similar changes in the basic processing machinery of the brain as a function of experience are seen also in somatosensory and motor cortices. Tactile discrimination training in monkeys increases the size of receptor fields for those areas of the skin surface most affected by training (Recanzone et al., [1992](#)). Moreover, training on a task emphasizing skilled movements of the digits of the hand to pick up small objects increases the representation of the hand in primary motor cortex, while training that emphasizes movement of the forearm to turn a key increases the representation of the forearm (Nudo et al., [1996](#)). Clearly, the networks that support basic perceptual processing in this domain are changed by experience.

Investigations with animals provide evidence that these changes within domain-specific processing occur via structural change – a rewiring of the brain, if you will. These changes include the creation of new synapses ([synaptogenesis](#)) in areas such as motor cortex. For example, rats that learned the acrobatic motor skills necessary to traverse an obstacle-filled course showed an increased number of synapses per neuron in motor cortex, an increase that correlated with the increase in performance (Kleim et

al., [1996](#)). In this case, as in the others just mentioned, the very brain systems necessary for the performance of a given task showed changes as a function of experience in that task, providing the substrate for procedural memory.

Evidence with humans also suggests that experience can alter the functioning of domain-specific processors. For example, in neuroimaging studies, the learning of specific finger-movement sequences resulted in changes in activation of various portions of the motor system critical for performance of that skill, including changes in the distribution of activation in motor cortex (Karni et al., [1995](#)) and the cerebellum (Jenkins et al., [1994](#)). This helps us better understand the abilities that are spared in amnesia, such as the rotary pursuit task (Grafton et al., [1994](#)), as well as in drawing or tracking tasks (Flament et al., [1996](#)). Learning such tasks relies on changes in motor cortex, a domain-specific processor. Similarly, [repetition priming](#) effects for visual materials are linked to changes in activation across visual processing regions. (e.g., see Buckner et al., [1998](#)). This conclusion is also supported by neuropsychological findings in two single-case studies of patients who had damage to extrastriate regions and impaired perceptual priming for visual materials (Gabrieli et al., [1995](#); Keane et al., [1992](#)). This deficit was selective, as neither patient showed difficulty in explicit remembering of the same visual materials, nor did they exhibit deficits in priming in other sensory modalities, such as audition.

In sum, domain-specific processing supports memory and learning in two distinct ways. First, the domain-specific regions encode and store a specific limited aspect of a particular experience or episode (e.g., just the sights, just the sounds). Each of the regions involved (e.g., visual cortex, auditory cortex) then becomes active again when that memory is retrieved. The hippocampus plays a critical role in binding together and associating the information from the different regions so that we can explicitly remember that event.

Second, incremental changes to the organization of these domain-specific processors can occur as a result of repeated exposure and experience, such as happens when learning a new skill, for example, how to juggle. These changes occur

independently of the hippocampus and are not linked to a particular event (e.g., my experience juggling four balls at 1 pm last Saturday). Rather, they reflect tuning and changes to the neural substrate supporting that ability that occur over time as a series of experiences (e.g., all the times I have practiced juggling) and generally occur implicitly, meaning that in some cases we may not even be aware that learning has taken place.

The Basal Ganglia: Skill Learning

In addition to domain-specific processors, another region of the brain that appears to enable implicit/procedural processing is the basal ganglia. Much of this knowledge initially came from neuropsychological studies of patients with either Parkinson's disease or Huntington's disease. These patients show a pattern of deficits opposite of that shown by patients with hippocampal damage – intact explicit/declarative memory with impairments in implicit/procedural memory. As we learned in [Chapter 4](#), Parkinson's and Huntington's diseases result from dysfunction of and damage to the striatum. Deficits in these patients therefore implicate these regions as critical for implicit/procedural learning.

Patients with Huntington's or Parkinson's diseases show deficits on many of the skill-learning tasks on which amnesics exhibit intact performance. These tasks are often characterized by [habit learning](#), which, while gradual and incremental, may not necessarily generalize to new exemplars. We were introduced to one task of this type earlier in the chapter: the rotary pursuit task, which involves tracking a target on a circularly moving platter with a handheld stylus. The striatal damage in patients with Parkinson's disease or Huntington's disease keeps them from having as large an increase in time on target as do neurologically intact individuals (Gabrieli, [1998](#)). In neurologically intact individuals, changes in activation of the striatum correlate with learning on this task (Grafton et al., [1992](#)).

Similar effects are observed in a serial reaction time (SRT) task, in which a number of different locations on a computer screen are flashed on each trial, and the individual

presses a button corresponding to that location. Unbeknownst to the individual, the locations are flashed in a particular repeating order. Even though people are not aware of the repeated sequence, implicit learning in this task is demonstrated both by individuals becoming faster over time at producing the repeating sequence, and also by the elongation of responding when the sequence is changed to a random order. In general, patients who have Parkinson's disease or Huntington's disease have difficulty in sequence learning (Doyon, [2008](#); Ruitenberg et al., [2015](#)). Converging evidence comes from functional neuroimaging work, in which activity associated with learning on this task (Grafton et al., [1995](#)), as well as on similar tasks such as finger sequencing (Seitz and Roland, [1992](#)), has been observed in the striatum.

At this point, you may have noticed that all the tasks discussed so far involve some sort of motor output, whether it be controlling one's limb to stay on a target in the rotary pursuit task or pushing a sequence of buttons in the serial reaction-time task. Therefore, you might be wondering whether the difficulties observed on these tasks in patients who have Parkinson's or Huntington's disease occur only because the basal ganglia play an important role in motor processing. This is certainly a reasonable question, but other evidence suggests that the difficulties generalize to other learning tasks that do not require a motor output (Shohamy et al., [2004](#)). One example is a deficit in the mirror-reading task exhibited by patients with Huntington's disease (Martone et al., [1984](#)). Relatedly, functional neuroimaging data indicate that learning to read mirror-reversed text as well as other skills is associated with activation of striatal regions among others (e.g., Poldrack and Gabrieli, [2001](#); Poldrack et al., [1999](#)).

Other evidence also implies that the role of the striatum in implicit/procedural learning is not restricted to the motor domain. Patients with damage to the basal ganglia are impaired at probabilistic learning tasks (Knowlton, Mangels, et al., [1996](#); Knowlton, Squire et al., [1996](#); Shohamy et al., [2004](#)). In these kinds of tasks, cues predict outcomes probabilistically, not in a one-to-one fashion, and the tasks must be learned via trial-and-error feedback. In one such task, the weather prediction task,

people are shown, on each trial, one to three cards from a deck of four (see [Figure 9.15](#)). On the basis of these cards, they must predict which of two outcomes (rain or shine) follows. Unbeknownst to the participant, each card is associated with the sunshine outcome only probabilistically: either 75%, 57%, 43%, or 25% of the time. When multiple cards are shown the outcome is associated with the conjoint probabilities of the cards. After making a choice, the participant is given feedback as to whether or not that response was correct. Gradually over trials, the participant learns the correct answers. The probabilistic nature of the task makes it somewhat counterproductive for people to attempt to recall specific previous trials, because repetition of any particular configuration of the cues could lead to different outcomes.

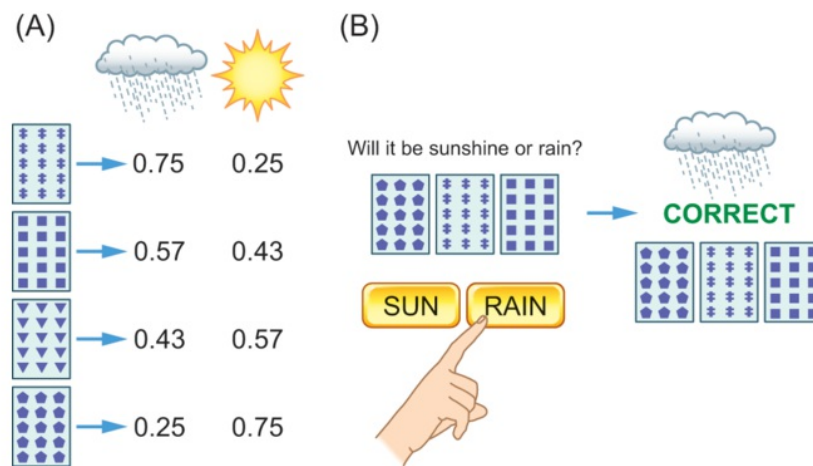


Figure 9.15 An example of a probabilistic learning task. Shown here is the weather prediction task.

(A) Each of four cards is associated only probabilistically with rain or shine. (B) Individuals are shown sets of one to three cards and must make a decision with regards to rain or shine. After making the decision, the participant is given feedback as to whether the answer was correct or not. Because the task is probabilistic in nature, particular configurations are not always associated with the same outcome. For example, when the first two cards are shown 66% of the time $[(.75+.57)/2]$ they are associated with rain and 33% of the time $[(.25+.43)/2]$ with sunshine.

(from Foerde and Shohamy, [2011](#))

Over a block of 50 trials, neurologically intact people showed significant and gradual improvement in their weather prediction performance, but patients with Parkinson's disease failed to show significant learning. Individuals with amnesia due to damage to the hippocampal regions perform as well as neurologically intact individuals, thus indicating that learning on this task is not dependent on hippocampal regions. Converging evidence for the role of the striatum in learning on such probabilistic tasks is provided by neuroimaging studies (e.g., Poldrack et al., [1999](#)). And a variety of other evidence, which we do not have room to review here, suggests that the striatum is fundamentally important for implicit/procedural learning, both in the motor and cognitive domains (for a review of evidence from both animals and humans, see Packard and Knowlton, [2002](#)).

Importantly, a characteristic of all the tasks that are supported by the basal ganglia is that individuals learn them via trial and error. As you may remember from [Chapter 4](#), the basal ganglia receive innervation from dopaminergic neurons. Studies in animals indicate that the release of dopamine can serve as a "learning signal." Single-cell recordings from the basal ganglia of monkeys indicate that cells innervated by dopamine show a particular pattern of firing related to whether an action leads to a reward or not (see [Figure 9.16](#)). When an animal receives a reward that is unexpected, dopaminergic cells show a large increase in firing rate compared to their baseline rate of firing. This signal may act as a learning mechanism telling the organism "Something good just happened! You might want to do it again." However, if a reward is expected, the cell's firing rate does not increase much, suggesting to the organism to maintain the status quo. Finally, if a reward is expected and it is not received, the cell's firing rate lowers substantially. Such a signal suggests to the organism that perhaps it might be time to change its response (Schultz et al., [1997](#)).

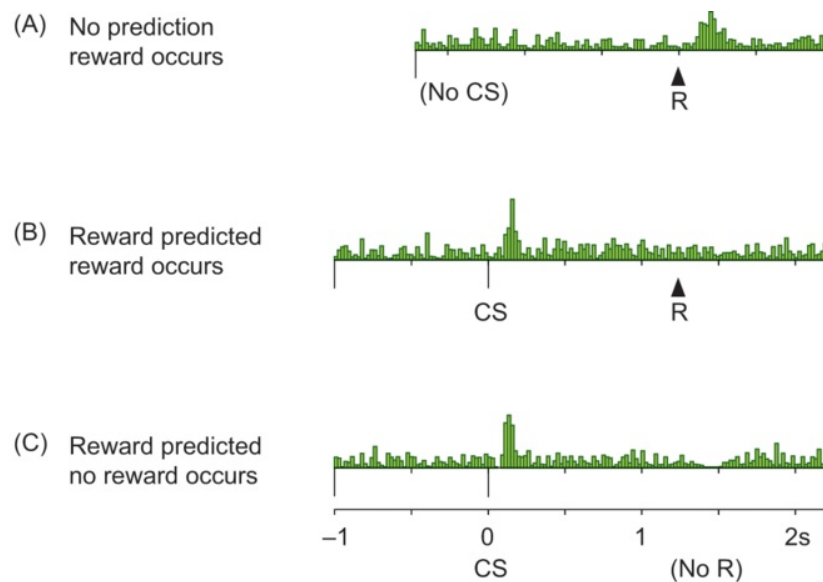


Figure 9.16 Dopaminergic cells fire in relation to whether or not a reward is expected, which acts as a learning signal.

Time is shown from left to right and bars indicate the degree of neuronal firing in an animal. The time at which a reward is received is shown by a dark line and the letter "R." (A) When a reward, such as a drop of juice, occurs unexpectedly (No CS), neuronal firing increases. (B) When the reward occurs, but a signal (CS) leads it to be expected, no increase in neuronal firing is observed. (C) When a signal (CS) leads a reward to be expected, but none occurs, neuronal firing decreases. Hence, neuronal firing acts as a learning signal indicating when the expectation of receiving a reward and the outcome are at odds.

(from Schultz et al., [1997](#))

Notice here that this mechanism aids in learning when the prediction between an expected outcome and the actual outcome are at odds. As such, it is sometimes referred to as error-driven learning, that is, learning is driven by an error between the expected and actual outcome. This error-driven learning mechanism tends to be implicit in nature – that is, individuals can learn from these action–outcome associations without being aware of them. Before we leave our discussion of dopaminergic learning signals in the basal ganglia, it is worth noting that such mechanisms can explain some of your own life experiences. For example, you may have experienced a rush the first time you kissed

someone you didn't think you were particularly attracted to, or found the taste of a recipe you thought you'd hate instead to be quite delicious. In both these cases, your dopaminergic cells were probably firing wildly to those unexpected pleasures. However, if you continue to see that person or eat that dish, you may have found that with time, those same experiences weren't quite as pleasurable. Because those rewards were expected, your dopaminergic cells were firing less, as there was not much new to learn. Correspondingly, these expected experiences become not quite so thrilling or enjoyable.

To summarize, all of what we have discussed suggests that the basal ganglia can make associations, for example, between stimuli or conditions and expected outcomes. But notice that the type of associations made by the basal ganglia are distinct from the associations made by the hippocampus. In general, associations made by the basal ganglia are between stimuli and responses, whereas the hippocampus makes associations across a variety of diverse neocortical processors. In the [final section](#) of this chapter, we return to this issue to consider other contrasts between the learning systems supported by the basal ganglia and those supported by the hippocampus.

The Amygdala: An Interface between Memory and Emotion

As we will discuss in more detail in [Chapter 12](#), the amygdala plays a large role in the analysis of affective information and the expression of emotional output. Here we emphasize its role as an interface between memory and emotion. The initial evidence for this role of the amygdala came from the amnesic patient H.M. His surgery, which included bilateral removal of his amygdala, left him with a decreased ability to access information about his internal states. In a systematic study of his responsiveness to pain and hunger (Hebben et al., [1985](#)), H.M. differed from other amnesic patients in whom the amygdala was intact, and from neurologically intact individuals, as he failed to identify pain stimuli as "painful" no matter how intense they were. He also failed to show changes in his ratings of hunger before and after meals. Indeed, on one occasion,

he rated his hunger as 50 on a scale of 0–100 both before and after a full dinner. Afterward, he was engaged in conversation with the experimenters and then given another full dinner. He did not remember the earlier dinner, ate the second dinner at his usual pace, and when done, still rated his hunger as 50.

Since those initial studies, we have learned that the amygdala plays two distinct and critical roles in the interaction of emotion and memory. First, it mediates the learning and expression of emotional responses to stimuli whose emotional significance is not automatic but has been learned via association. Second, it allows emotional experience to modulate certain aspects of long-term memory. Each of these roles is discussed in turn.

The amygdala is critically involved in emotional memory and the learning of emotional responses. Perhaps the best-studied example of emotional memory involves the brain system that mediates Pavlovian [fear conditioning](#) (e.g., LeDoux, [2000](#)), in which a stimulus comes to invoke fear because it is paired with an aversive event. For example, rats are placed in a chamber in which they are presented multiple times with a 10-second pure tone that is terminated with a brief electric shock through the floor of the cage. They come to exhibit conditioned fear to the subsequent presentation of just the tone, because it was paired with the shock. This fear is expressed by changes in autonomic responses, such as arterial blood pressure; in motor responses, such as stereotypic crouching or freezing behavior; and in suppression of the urge to drink sweetened water, which rats usually like. Animals with selective lesions in the lateral amygdala show dramatically reduced conditioned autonomic and motor responses to the tone.

Intact animals also exhibit [contextual fear conditioning](#), meaning that their fear response is selective to the context, or environment, in which conditioning occurs. When intact rats are again placed in the conditioning chamber after initial exposure, they begin to freeze even before the tone is presented. Their reactions have been conditioned both to the tone and to the environmental context in which tones and shock have been paired. If placed in a different environment, they do not freeze unless a tone is presented.

Amygdala lesions block this contextual fear conditioning, just as they block Pavlovian fear conditioning (see [Figure 9.17](#)).

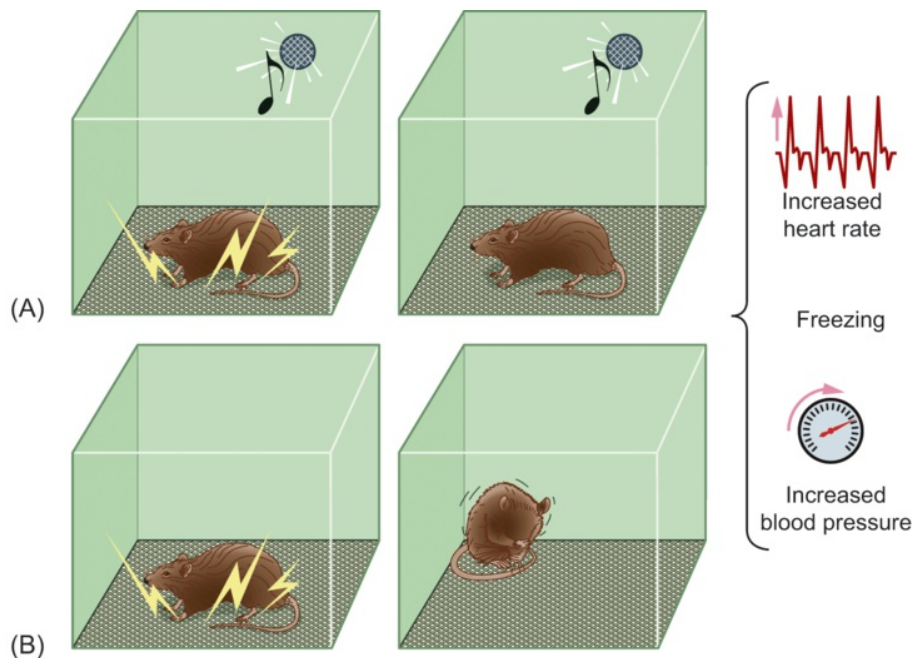


Figure 9.17 Illustration of fear conditioning and contextual fear conditioning.

(A) In fear conditioning, a formerly neutral signal, such as a tone of a particular frequency, is paired multiple times with a shock. As a result, when neurologically intact animals hear just the tone, they express fear, as reflected in increased blood pressure, freezing, and suppression of typical behaviors, such as drinking sweet water. (B) In contextual fear conditioning, animals associate the conditioning chamber with the shock even before a tone is presented. Animals with amygdala lesions show neither of these responses.

Converging evidence for the role of the amygdala in emotional learning is provided by studies in humans (Phelps and LeDoux, [2005](#)). For example, fear conditioning is associated with increased activation of the amygdala as measured by fMRI, and the larger the amygdala activation, the stronger is the conditioned fear response (Phelps et al., [2004](#)). Damage to the amygdala precludes individuals from exhibiting a conditioned fear response. Nonetheless, if their hippocampus is intact, they can report the particulars of the conditioning paradigm, such as that a specific tone was paired with a shock. In

contrast, individuals with hippocampal damage will show the appropriate physiological response to fear conditioning, although they cannot recall the particulars of the conditioning paradigm (Bechara et al., [1995](#); LaBar et al., [1995](#)). Stimulus-reward learning is also disrupted in humans with amygdala damage (Johnsrude et al., [2000](#)).

The second contribution of the amygdala to memory involves the modulation of memory by emotional experiences. Strong evidence for this comes from a paradigm developed by Cahill and colleagues for studying human memory ([1995](#), [1996](#), [1999](#)). Their test involves presentation of a single series of slides and two alternative narratives, one of which is emotionally charged (e.g., a story about a mother and son involved in a traumatic accident), and one of which is not (e.g., a story about a safety drill). In subsequent delayed-memory testing, neurologically intact people showed a selective enhancement of recall for the emotional component of the tragic story but not the analogous portion of the neutral story. Bilateral damage to the amygdala in a patient with Urbach–Wiethe syndrome selectively wiped out the enhancement of memory for the emotional part of the tragic story, but did not affect memory for the neutral components of the story. This damage also did not prevent such individuals from appreciating the emotional content of the tragic story. Moreover, when viewing emotionally intense stimuli, the greater the degree of activation of the amygdala is for a particular item, the better the subsequent recall of that item (Canli et al., [2000](#)).

The amygdala is thought to exert such an influence over memory through its interaction with many structures involved in memory processing that we have already discussed, such as the hippocampus and striatum, and other regions, such as frontal cortex, that we discuss in subsequent portions of this chapter (see LaBar and Cabeza, [2006](#), for a review). As we learn in more detail in [Chapter 12](#), the amygdala is thought to respond to emotional situations that are highly arousing. When it becomes active, it in turn influences portions of the memory circuitry in the brain. Thus, at least a portion of the amygdala's action on memory can be thought of as modulating activity within the memory circuitry as a function of arousal. Such a mechanism, as you might imagine, is quite adaptive. Highly arousing situations are often those that can be important for

survival, such as when one encounters a serious threat. Having a mechanism that enhances memory for such situations is obviously advantageous.

Anterior Temporal Regions: Amodal Storage of Semantic Information

To appreciate the role that anterior temporal regions play in memory, we need to consider that the ability to explicitly recall information or events is not limited just to specific episodes in our lives. Rather explicit/declarative memories can be divided into two types: episodic memory and semantic memory (Tulving, [1972](#)). [Semantic memory](#) refers to knowledge that allows us to form and retain facts, concepts, and categories, both about the world and about the people we know, such as where they live, their occupations and interests, and their personality characteristics. Such information is not linked to a specific episode but rather pertains across many different episodes and context. In contrast, as we have discussed, episodic memory refers to autobiographical memories about specific episodes in our lives and includes information about the time, place, and circumstances of a given specific experience.

To make this distinction clearer, consider an example of an episodic memory, the memory of your first kiss. This memory includes information about the person whom you kissed, the place where it occurred, how you felt, and so forth. In contrast, your semantic memory about kisses includes information such as that they involve the placing of a person's lips on someone else or an object; are used to demonstrate ardor, affection, or appreciation; and are commonly given when people are meeting one another or when they are leaving. In this example, whereas information contained in semantic memory is about kisses in general, that contained in episodic memory is about a particular kiss. Episodic memory allows a reexperiencing of the event – providing the opportunity, in essence, to travel back in time (Tulving, [1985](#)) whereas semantic knowledge allows us to generalize knowledge across time.

As we have discussed earlier in this chapter, people with damage to the medial temporal lobe lose the ability to form new memories about episodes in their lives, suggesting a disruption of episodic memory. However, after injury they can learn at least

some new semantic information, suggesting that semantic memories may not rely entirely on the medial temporal region (e.g., Bayley et al., [2008](#)). One of the most dramatic examples of such learning comes from three case studies of children who sustained damage in childhood (at birth, age 4, and age 9) that included portions of the hippocampus (Vargha-Khadem et al., [1997](#)). Despite having a pronounced amnesia for the everyday episodes that occurred in their lives, they were nonetheless able to attend mainstream school, at which they learned language skills (including the ability to read) and enough factual information to place their intelligence within the low average to average range.

Nonetheless, these cases are extreme ones in which the brain may have adapted developmentally to the lack of a hippocampus. We should not take too far the idea too far that new semantic information can be acquired totally independently of the hippocampus. In fact, as we have discussed, after his surgery H.M. was not able to acquire new information about occurrences in the world, such as what an astronaut is, which clearly falls into the domain of semantic processing. Nonetheless, retrieval of semantic information may be somewhat possible without the hippocampal system.

How might that occur? At least some aspects of semantic memory may rely on domain-specific neocortical processors. For example, your memory of the feel of wool is likely to be aided by reactivation of somatosensory regions, whereas your memory of the shape of sheep is likely aided by reactivation of visual areas (Binder and Desai, [2011](#)).

But what about semantic information that is not linked to a particular modality? Anterior temporal lobe regions may play a role in retaining such information (Simmons and Martin, [2009](#)). Some evidence for this viewpoint comes from a disorder called [semantic dementia](#), in which patients progressively lose the ability to retain semantic information. For example, when traveling through the countryside to visit a friend, a patient with this disorder reminded his wife where to turn to reach their friend's house, but then looked at sheep in a field they were passing and asked her, "What are those

things?” The most notable pathology in this disorder is degeneration of the anterior temporal regions. Similarly, repetitive transcranial magnetic stimulation over anterior temporal regions in neurologically intact people slows the ability to name pictures (e.g., swan, poodle) and to pick synonyms for words (e.g., shown “rogue,” choosing “scoundrel” rather than “polka” or “gasket”). However, it does not interfere with nonsemantic judgments, like naming numbers or determining which numbers are closest in value (e.g., shown “36,” picking “40” as compared to “30,” “42,” or “28”) (Pobric et al., [2007](#)). Supporting evidence is provided by functional neuroimaging, which indicates activation in this region during tasks requiring semantic processing (Binney et al., [2010](#); Patterson et al., [2007](#)).

Why, from a neuroanatomical position, would anterior temporal regions be well positioned to support amodal semantic processing? Similar to the hippocampus, this region may serve as a convergence zone. But unlike the hippocampus, which is binding together information about specific episodes in time, the anterior temporal region is integrating sensory input from modality-specific regions with regards to specific episodes. For example, information from visual regions about the visual form of sheep and information from somatosensory regions about the feel of wool converge onto the anterior temporal lobe. As such, this region can over time codify and elaborate information about sheep in general such as that they look “puffy” because of their wool; that wool is warm; that because of its warmth, people use wool in clothing and so forth (Binder and Desai, [2011](#); Rice et al., [2015](#)) (see [Figure 9.18](#)).

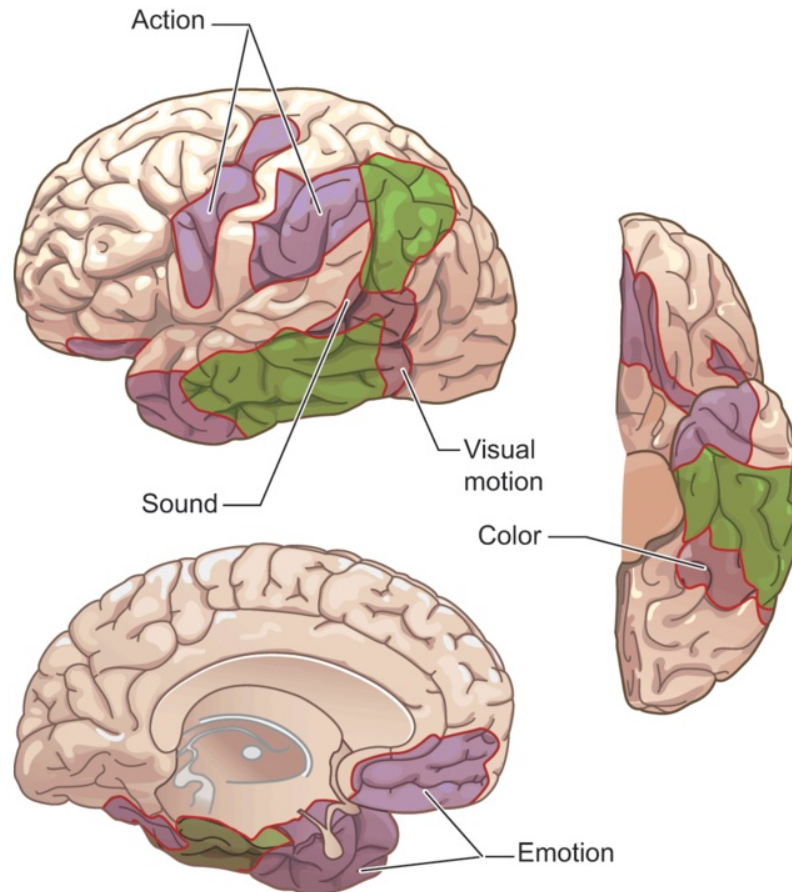


Figure 9.18 Amodal semantic regions in the anterior temporal lobe receive input from modality specific processors.

Regions involved in modality-specific processing (shown in purple) send information that converges in anterior temporal regions (shown in green) to create amodal semantic representations of information

(from Binder and Desai, [2011](#)).

Brain Systems for Different Stages of Memory

So far we have spent some time discussing different types of memories: declarative memories, both episodic and semantic; implicit memories, including skills and habits; and emotional memories. Yet another way to understand memory is to break it down, not by the type of memory, but by the different processing stages that are involved in memory. First, memories have to be created – that is, information must be encoded into memory. Memories also must be stored, or maintained over time. While they are stored,

they may undergo consolidation, or strengthening. Finally, for a memory to be useful we need to be able to access it; that is, we need to be able to retrieve it. In this section, we examine which regions of the brain make these processes possible.

Before we do so, however, it is important to realize that we need converging evidence from various techniques to identify the critical brain regions for each of these processes. For example, consider the limitations of work done solely on individuals with amnesia. Deficits in memory seen at some lengthy delay after learning could reflect impairment in any of these stages of memory. Impairment in the initial encoding of memories could prevent information from being fully processed or from being stored in a robust enough form to allow for later retrieval. Alternatively, impairment in the storage, maintenance, or consolidation of memories could cause information to decay abnormally rapidly over time, limiting the patient's ability to remember them. Finally, impairment could occur in the retrieval of memories despite normal storage and maintenance of the information. No definitive answer about which of these stages is the locus of the impairment in amnesia can be provided by studies of these patients alone. Nevertheless, the results of these studies, taken together with newer methods in cognitive neuroscience, have provided a more complete answer in identifying the brain systems that exert their effects at multiple times in the lifetime of a memory: at encoding, during storage and consolidation, and at retrieval.

Encoding: The Medial Temporal Lobe and Prefrontal Regions

A variety of studies, including a meta-analysis of neuroimaging data (Spaniol et al., [2009](#)), indicate that two major brain regions play a role in encoding: the medial temporal lobe and prefrontal cortex. As you may have noted throughout the chapter, while we have focused on the hippocampus we have often said “the hippocampus and associated medial temporal lobe structures.” At this point, it is worth a slight diversion to discuss how these associated medial temporal regions might play a role in memory

encoding, as their activity is often noted in neuroimaging studies during encoding and damage to them results in memory deficits.

[Figure 9.19](#) shows the location of the hippocampus vis-à-vis other medial temporal lobe regions. Regions of the hippocampus are abutted from posterior to anterior by retrosplenial cortex, parahippocampal gyrus, perirhinal cortex, and the entorhinal cortex. As you may remember from [Figure 9.4](#), information enters the hippocampus at its most anterior end via the entorhinal cortex. It has been suggested that processing of information in these adjacent cortices serves as “pre-processors” if you will of the information that gets bound together as an episode within the hippocampus proper. There are currently a variety of models that suggest differential roles for exactly what type of information each region may be contributing to this binding process and the nature of the representation of such information. The nuances of these models are beyond the scope of the current discussion (e.g., Rosenbaum et al., [2014](#); Ranganath and Ritchey, [2012](#)).

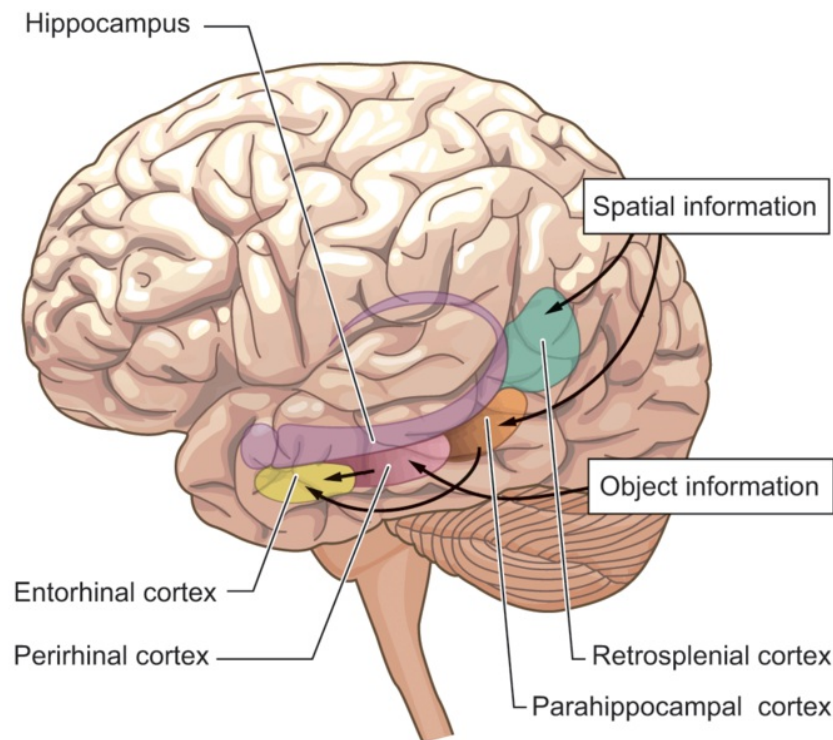


Figure 9.19 Regions of the medial temporal lobe associated with the hippocampus that also play a role in encoding.

Retrosplenial cortex and the parahippocampal gyrus process spatial information, while the perirhinal cortex processes information about objects, and the entorhinal cortex processes amodal semantic information.

Nonetheless, there is agreement that distinct portions of these adjacent regions may help in the encoding (and potentially retrieval) of information. Retrosplenial cortex has been suggested to process spatial information (Vann et al., [2009](#)) along with the parahippocampal gyrus, which you may remember from [Chapter 7](#) is the location of the parahippocampal place area that processes information about location. Perirhinal cortex is thought to process information about objects and their identity (Suzuki and Naya, [2014](#)). Such information is sent along to the entorhinal cortex, which as we discussed above is involved in the representation of amodal semantic information. All of this information can then be transmitted to the hippocampus via the entorhinal cortex (see [Figure 9.19](#)). These associated medial temporal lobe structures appear to play an important role in encoding. Not surprisingly, compared to damage that encompasses just

the hippocampus, damage that extends beyond the hippocampus to these associated medial temporal lobe structures leads to a particularly profound amnesia (e.g., Insausti et al., [2013](#)).

However, rather than just observing activity in the hippocampus and other medial temporal lobe structures, we might desire evidence that such activation plays a central role in the successful encoding of an item. Stronger evidence for such a role is provided by studies of the [subsequent memory effect](#): subsequently remembered items are associated with greater brain activity at encoding than items that are not subsequently remembered. This effect was first demonstrated using ERPs, in which activity recorded at the scalp at the time of encoding predicted subsequent memory performance (e.g., Paller et al., [1987](#); Fabiani and Donchin, [1995](#)). At the time that research was done, it was not possible to identify the particular brain systems that produced the effect. However, subsequent work using depth recordings in the hippocampus yielded the same ERP effect (Fernandez et al., [1999](#)), suggesting that the hippocampus is the likely neural source of such activity. Finally, fMRI studies have demonstrated that the amount of hippocampal activity at the time an item is first seen and encoded predicts how well that item will be remembered later on (Brewer et al., [1998](#); Wagner et al., [1998](#)), and effect that has been shown to be very replicable (Kim, [2011](#)). Taken together, this work illustrates that the hippocampal system is active at the time information is encoded into memory, and that this activity is predictive of how well that information will be remembered.

But what process is the hippocampus undertaking during encoding of memories besides linking up or conjoining the distinct pieces of an event? One challenge with regards to memories is the need to distinguish clearly between different episodes. For example, say that you have a favorite restaurant and, to impress someone, you often go there for a first date. Obviously to avoid any embarrassing conversations, you will need to clearly differentiate the first date there with your current romantic partner from your previous first dates there with prior romantic partners. Notice that this may be difficult because certain aspects of the experience are likely to be highly overlapping: the spatial

location is highly similar, you may have ordered your favorite dish both times, you may have asked similar questions to learn more about the person and so forth. Researchers have argued that portions of the hippocampus are important for what is termed pattern separation, whereby highly similar and overlapping representations are encoded in a way such as to make them more distinct (Yassa and Stark, [2011](#)).

Evidence for pattern separation in the human hippocampus comes from neuroimaging studies in which people learn specific items. Then later on they are shown either the identical item as previously viewed (i.e., repeated), a “lure” that is quite similar yet distinct from the original item, and new (i.e., novel) items. Researchers examined whether the neural response to each item was attenuated compared to the original presentation, which would indicate that the brain was treating an item as similar to the original presentation (refer back to Chapter 6, page [179](#) for similar logic in studies of object constancy). While some portions of the brain showed an attenuated response to both the repeated items and the lures due to their high degree of similarity, the CA3 region of the hippocampus did not, treating the lures as if they were entirely new items and distinct from those previously viewed (Bakker et al., [2008](#)). Furthermore, intracranial recordings in humans have shown that the activity in certain subgroups of human hippocampal cells also clearly distinguishes lures from previously viewed items (Suthana et al., [2015](#)), supportive of the idea that the hippocampus plays a role in pattern separation during encoding.

Prefrontal regions, in particular the ventrolateral prefrontal cortex and the dorsolateral prefrontal cortex, are also involved in encoding. These regions show robust activation at the time of encoding. Like the hippocampus, their specific involvement in encoding is demonstrated by neuroimaging studies of subsequent memory effects (Spaniol et al., [2009](#)). As observed for the hippocampus, activation is greater in these prefrontal regions at the time of encoding for items that are subsequently remembered than those that are not. In contrast to the hippocampus, however, these prefrontal regions appear to be important for strategically mediated aspects of memory encoding, which is enabled by their role in working memory (to be discussed in more

detail later in the chapter). These regions are thought to aid in the focusing and organizing of memory encoding, by inhibiting irrelevant information and arranging relevant information in such a way that it can later be easily retrieved.

The contribution of the ventrolateral prefrontal cortex to encoding can be shown to be distinct from that of the hippocampal system, as normal activation of the ventrolateral prefrontal cortex is seen even in patients with hippocampal system damage, who exhibit severely impaired memory (Dupont et al., [2000](#)). Ventrolateral prefrontal regions may aid in selecting information that is most relevant for encoding from among the many features or pieces of a given episode. They may also aid in keeping irrelevant information from interfering from the critical information to be encoded (e.g., Jonides and Nee, [2006](#)). Supporting such an idea, transcranial magnetic stimulation over ventrolateral prefrontal cortex, which disrupts activity in this region, causes an increase in the report of false alarms in tests of recognition memory. People incorrectly indicate that an item had appeared when in fact it had not, suggesting that irrelevant information is interfering with memory (Blumenfeld et al., [2014](#)), indicating decreased ability to focus on relevant information and/or suppress distracting information.

Another prefrontal region, dorsolateral prefrontal cortex, which is important for working memory, may also contribute to encoding. It seems to be especially important for encoding information when that information must be reordered or rearranged as to best enable encoding and retention (Blumenfeld and Ranganath, [2006](#)). This region may aid encoding by holding together multiple pieces of information at the same time, which would then, in turn, enhance their ability to be bound and associated in long-term memory (see Blumenfeld and Ranganath, [2007](#), for a review of prefrontal contributions to encoding).

To better understand the contributions of different brain regions to encoding, imagine that you have gone shopping with your friend and have found a shirt that you want to buy. However, you have left your credit card in your car and will need to leave the store to retrieve your credit card and come back to purchase the shirt. Your hippocampus will bind together all the disparate pieces of the event of finding the shirt you want to buy –

the fact that you had just been looking at jeans when you saw the shirt, what the shirt looks like, where in the store it is located, what your friend said about the shirt, the other shirts on nearby racks, what music was playing in the store, that a salesperson was helping someone near you, and so forth. What your ventrolateral cortex is likely to do is to help you to focus on the critical information about the shirt (e.g., what it looks like) and filter out the extraneous information about the event (e.g., the fact that you had previously just been looking at jeans, what music was playing in the store; that a salesperson was helping someone near you) that is unrelated to your desire to purchase the shirt. Your dorsolateral prefrontal cortex is likely to aid in organizing the relevant information to enable you to find the shirt when you return from the car by carefully linking together the attributes of the experience that will enable you to do so – where in the store the shirt was located, what the shirts on other nearby racks look like, and then the attributes of the shirt you want to purchase.

Consolidation and Storage: How Critical Is the Hippocampus?

Some theories suggest that the hippocampus also plays a role in [memory consolidation](#), the process by which memories are strengthened to allow for long-term retention. This process may be ongoing from minutes to days after a memory is laid down (for review see Dudai et al., [2015](#)). The notion that memories may undergo consolidation comes from clinical observations of retrograde amnesia, which is characterized by an inability to remember events for some period prior to the injury. We can assume that prior to the injury the hippocampal system was working perfectly fine and that events should have been encoded normally. Yet, the ability to recall those memories is compromised, suggesting that those memories were in a fragile state, and that processing of memories continues even past the stage of initial encoding.

Evidence supporting a period of consolidation comes from the fact that the temporal extent of retrograde amnesia changes as the time since injury passes, as is often observed after a closed head injury (Squire, [2006](#)). This phenomenon is often referred to as shrinking retrograde amnesia. Generally, immediately after the injury, the

retrograde amnesia covers an extended period of time. Because the brain has just sustained an insult, memory retrieval is difficult. But as hours and days pass post-injury and the brain recovers, the retrograde amnesia shrinks so that memories of the more remote past can be accessed and the retrograde amnesia covers only the most recent period of time (see [Figure 9.20](#)). For example, immediately after an injury a person may not remember what happened in the 20 minutes prior. However, after a couple of days, the temporal extent of retrograde amnesia will diminish. It may extend back in time only to 5 minutes prior to the injury. However, memories from the time period just prior to the injury are never recovered. (For this reason, people who have been involved in accidents that have caused head injury, even minor ones, often cannot say what caused the accident.)

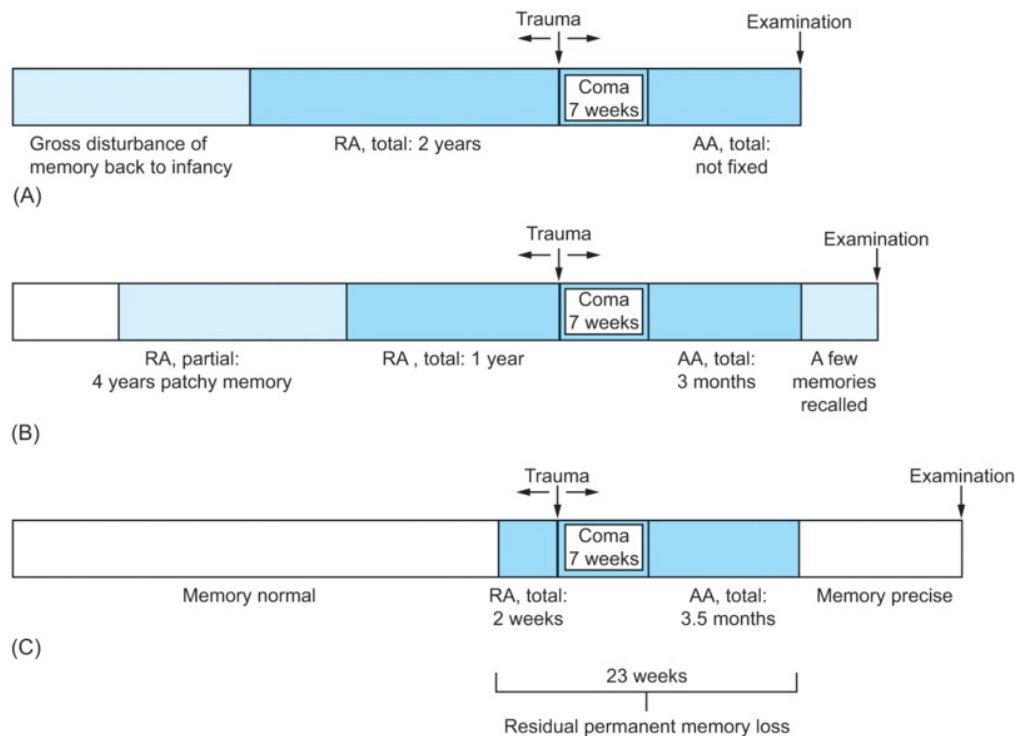


Figure 9.20 Illustration of the phenomenon of shrinking retrograde amnesia.

The memory status of a patient was assessed at three examination times: (A) 5 months, (B) 8 months, and (C) 16 months after closed head injury. The time of the head injury is indicated by the vertical line labeled Trauma in each timeline. The portion of time for which memory was impaired is depicted in blue, and times of patchy impairment are represented by lightly shaded areas. The portions of time affected to the right of the vertical line indicate the extent of the anterograde amnesia. The portions of time affected to the left of the vertical line indicate the extent of the retrograde amnesia. Across the three timelines, the retrograde amnesia shrinks from an initially extensive impairment encompassing years to a more limited amnesia affecting only weeks.

The degree to which the hippocampus is required for consolidation remains an issue of debate. One model, known as the consolidation model, argues that the hippocampal system is required not only to lay down memories, but also to consolidate them. In this consolidation process, the hippocampus aids, over time, in strengthening the bonds between the distinct pieces of a memory trace, each of which relies on a separate neocortical processor. Once they are bound in this way, they can be retrieved

independently of the hippocampal system (Squire et al., [2004](#)). As an analogy, imagine that you introduce two friends to one another. At first, they might only see one another when the three of you get together. However, over time you help to establish a relationship between the two of them, so that eventually they can get together on their own without your help. In a similar way, the hippocampus may act over time to establish a relationship between different pieces of a memory that are stored in different cortical units. Once the relationship is established, the hippocampus can be removed from the picture without damaging the relationship.

This model explains the temporal gradient of retrograde amnesia, in which more recent memories are more affected than more remote memories (Brown, [2002](#)). The events at time of insult were not consolidated at all, and so they can never be retrieved. More recent memories were only partially consolidated prior to the insult, so damage to the hippocampus precludes full consolidation and results in compromised memory. In contrast, much older memories have already been consolidated and are unaffected by hippocampal damage – they no longer require the hippocampus and essentially reside in other portions of the cortex (Squire et al., [2015](#)).

Another model, the multiple trace theory (Nadel and Moscovitch, [1997](#); Moscovitch et al., [2005](#)), argues that there is no prolonged consolidation period. Rather, the hippocampus is obliged to encode the different aspects of any experience and bind them together, a process that occurs in a matter of seconds or at the most days. Rather than a process of consolidation, the multiple trace model argues that every time a memory is retrieved, the hippocampus creates a new trace indexed to that event – hence the name “multiple trace” theory. For example, when you learned about specific events involving Pope Francis, such as him saying he was not one to judge gay people, you likely also retrieved your memory of him being selected as Pope, laying down another trace for that prior event in the hippocampus. In this manner, old memories will be represented by a stronger set of hippocampal-neocortical traces than new ones. Thus, older memories are less susceptible to disruption from brain damage than memories that have been created

more recently. According to this model, when these autobiographical or episodic traces are related, the relationship facilitates the extraction of information that is common among all of the traces of these events in neocortical regions. For example, as you acquire more memories of specific events involving Pope Francis, you are able to generalize across events to specific characteristics you associate with him that are likely linked to information in specific neocortical processors, such as the visual shape of his smile or the auditory characteristics of his voice. With time this information is then bound together with semantic knowledge to create memories that are independent of the hippocampus. For example, your memory of Pope Francis bending over and kissing a disfigured worshipper is linked to your semantic knowledge regarding the Pope's concern about the welfare of the weakest and most disadvantaged among us.

The argument here is that the nature of the memory trace can shift, from one that is specific to an episode to one that is represented in a more schematic version that contains the gist of the memory. It is this prolonged process of memories morphing from a more detailed episodic memory to one of a more schematic nature that gives the impression of a prolonged consolidation process. (Because of this morphing of memories, the multiple trace theory is now more often referred to as the transformation hypothesis.) While the schematic aspects of a memory can be linked to information in neocortical processors, this theory argues that the hippocampus is always required to recall the detailed specific attributes of a given episode because only it stores a pointer to the various representations distributed across the cortex that define that episode. Hence, the hippocampus is critical for episodic memory, and its involvement does not vary with the age of the memory.

Researchers continue to debate the merits of the consolidation versus transformation hypotheses (Squire and Bayley, [2007](#); Winocur and Moscovitch, [2011](#)). For example, research with some amnesic patients has suggested that all autobiographical memories are affected regardless of their remoteness (e.g., Noulhaine et al., [2007](#); Steinworth et al., [2005](#)), a finding consistent with the transformation hypothesis; but a meta-analysis across studies suggests that the more typical pattern is a graded decrement (Brown,

[2002](#)). Likewise, whereas some neuroimaging studies show greater activation of medial temporal regions in older adults for recent as compared to remote memories (e.g., Haist et al., [2001](#)), consistent with the consolidation theory, others do not find variations with regard to the age of the memory (Maguire et al., [2001](#)), consistent with the transformation hypothesis.

These studies illustrate how complicated the issues regarding the neural bases of memory can be. One of the reasons why memories are so important in our daily life is that not only do we encode them, but we also retrieve them and connect them with the rest of our experience. What this means, and what is reflected in both theories, is that memories are unlikely to remain static. Rather, they are transformed over time by our subsequent experience and the new memories that we acquire.

Retrieval: Hippocampal, Prefrontal, and Parietal Mechanisms

Of course, it's no good to encode and store memories unless we can retrieve them when we need them. As we will see, although retrieval is a separate mechanism from encoding and storage, several of the same brain regions, notably the hippocampus and prefrontal cortex, aid in retrieval, as does the left parietal cortex. We discuss the contributions of each of these three regions in turn.

The Role of the Hippocampus in Retrieval

Neuroimaging evidence indicates that activity in the hippocampal system occurs across a wide variety of retrieval conditions, including those requiring recall of episodic, semantic, and autobiographical information (Burianova, McIntosh, and Grady, [2010](#); Ryan et al., [2008](#)). However, the portion of the hippocampus involved in retrieval may be somewhat distinct from that involved in encoding (Eldridge et al., [2005](#)). Meta-analyses across PET and fMRI studies suggest that more anterior regions of the hippocampus are engaged for encoding of episodic memories, while more posterior regions are involved in retrieval (see Lepage et al., [1998](#); Spaniol et al., [2009](#)).

The exact nature of the processes or operations being performed by the hippocampus at the time of retrieval is still somewhat of a mystery. Nonetheless, there is evidence that the hippocampus participates in the reactivation of long-term memories. When some aspect or component of an event is experienced later in time, the hippocampal system allows for retrieval by linking that component with other component pieces, each of which is stored in distinct neocortical processors (e.g., Staresina et al., [2013](#)). In this manner, the hippocampus can be seen as allowing for **pattern completion** – one smaller piece of information can be used to reconstitute the whole (see Halgren, [1984](#); Eichenbaum, [2000](#)). You may have an intuitive sense of how this pattern completion works from your own experiences. For example, you may be heading out the door for the day and find that you don't have your keys. By thinking back to the point in time at which you last walked into your house or apartment, a relatively small piece of information, you may be able to reconstitute the entire episode including where you placed your keys.

Evidence for such pattern completion comes from neuroimaging studies in which multi-voxel pattern analysis is used to ascertain the pattern of activity over the hippocampus during encoding. In one such study, people learned to classify specific nature scenes as falling into one of two random categories (A versus B), and the multi-voxel pattern analysis in the hippocampus associated with each category was determined (Bonnici et al., [2012](#)). People were then shown 50/50 morphs between the two scenes and had to judge whether the morph fell into category A or category B. If the decision is being made totally on the basis of perceptual information, the multi-voxel pattern should look like a blend of the two patterns. But if the hippocampus is doing pattern completion, then the multi-voxel pattern should mimic one of the two categories. The researchers observed that if the person judged the 50/50 morph as belonging to pattern A, activity across the hippocampus was more similar to the multi-voxel pattern analysis associated with Category A than Category B. Conversely, if they judged the 50/50 morph to belong to pattern B, the pattern of activity was more similar to the multi-voxel pattern analysis associated with Category B than Category A. Here we can see

that the hippocampus takes some perceptual features from the 50/50 morph and uses them to complete the rest of the information for a given category.

Some evidence suggests that the hippocampus' involvement in memory retrieval may vary depending on the manner in which information is retrieved. Some researchers have argued that recall of an item, as well as the recognition that an item has been seen before, rely on the same fundamental processes, but that the confidence one has or the strength of information is greater for recall than recognition (e.g., Dunn, [2004](#)). However, other psychologists have argued that two separate and distinct processes occur in memory retrieval. These models, known as dual-process models (for reviews, see Yonelinas, [2001](#); Yonelinas et al., [2010](#)), argue that recognition relies on the strength of undifferentiated information about the item or event, or, said more simply, a sense of familiarity. In contrast, recall involves remembering something specific about the item, such as the instance or episode in which the information was first learned. In memory studies, experimental psychologists often ask people to differentiate the type of memory they have for an item by asking at test whether the person is familiar with and “knows” that he or she has seen the item before, as opposed to recalling the specific item and “remembering” that he or she has seen it before.

Electrophysiological studies supply evidence for distinct neural signatures of each of these processes, suggesting that they are indeed separable. In a typical experiment, people see a list of items to remember. Afterward, they are given a list of items and must decide whether they have seen the word before or not. Included in the list are new words, known as lures. Some of the lures are very dissimilar to words on the initial list. Others, however, are quite similar (e.g., “trucks” as compared to “truck”). Not surprisingly, people often report having seen these similar lures before, resulting in a false alarm. One component, recorded maximally over parietal regions of the brain at about 600 ms post-presentation as a positive deflection, is greater to a correctly recognized item than to either similar lures that individuals claim they have seen before or dissimilar lures that they correctly identify as new. Notice that this component

distinguishes between items indeed seen before from those not seen before, regardless of what an individual reports he or she has seen!

This old/new parietal component may be indexing processes that are required when a person really remembers an item, such as accessing information about the spatial and temporal context in which the item was learned. In contrast, a negative component is recorded over frontal leads at about 400 ms that is larger for correctly rejected new words than for items that an individual thinks he or she has seen before, regardless of whether that is the case (e.g., studied items correctly identified as old and similar lures incorrectly identified as old) (see [Figure 9.21](#); Curran, [2000](#)). This component may reflect the familiarity component of memory retrieval (see Rugg and Curran, [2007](#), for a longer discussion of what ERPs can tell us about recognition memory). Converging evidence from neuroimaging studies and patients with circumscribed brain lesions also suggests that different neural systems are engaged by familiarity and recollection (Skinner and Fernandes, [2007](#)).

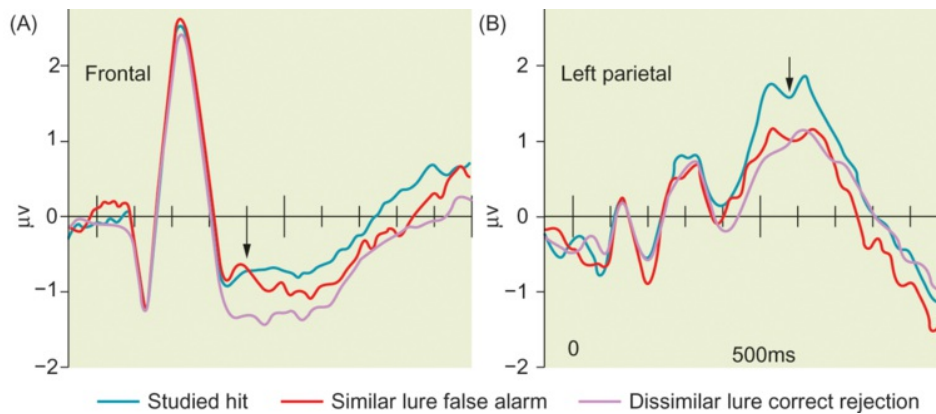


Figure 9.21 Event-related potentials that index different memory processes.

(A) The left frontal negativity indexes the process of familiarity. This component is greater for those items that the individual perceives as being new (dissimilar lure correct rejection) than for the item the individuals thinks he or she has seen before, regardless of whether the items are indeed old (studied hits) or not (similar lure false alarm). (B) In contrast, a left parietal component indexes the process of recognition. It is larger for items that individuals report as having seen previously (studied hit) than for items they have not seen, regardless of whether they report the item as being old (similar lure false alarm) or new (dissimilar lure correct rejection).

In addition, it is suggested that each of these processes relies on distinct neural substrates. As we have discussed in detail earlier in the chapter, results from patients with damage to medial temporal lobe structures and neuroimaging studies suggest that the hippocampus and related midline diencephalic structures (e.g., mammillary bodies, anterior thalamic nuclei) are required for specifically remembering an item or event along with the complexity of its larger spatial and temporal context. Retrieval processes associated with familiarity, in contrast, are proposed to rely on the nearby perirhinal cortex and connections with the dorsal medial nucleus, which are likely to have representations that are not as precisely pattern-separated as those of the hippocampus (for a review, see Eichenbaum et al., [2007](#); for a dissenting viewpoint, see Wixted and Squire, [2011](#)).

An intriguing recent hypothesis suggests that the distinct nature of representations underlying recognition, compared to familiarity, can influence how we forget (Sadeh et

al., [2014](#), [2016](#)). Because hippocampal representations during encoding are designed for maximal pattern separation, they may be relatively robust to interference from the learning of new items. As we discussed before, the hippocampus does a good job of separating and distinguishing between items and closely associated lures. However, physiological research suggests that even in adults there can be neurogenesis of granule cells in the hippocampus, meaning that hippocampal circuits undergo remodeling. This remodeling may make it difficult to then reconstitute a memory via pattern completion (since the underlying neural circuitry required has been altered). As a result, with time, recognition memory will decay. In contrast, representations underlying familiarity are more overlapping and less distinct, as exemplified by the research with lures that we discussed above. While such a mechanism allows new representations to be integrated with similar previous ones, the downside is that representations associated with familiarity are subject to interference from similar experiences or items, and forgetting will be driven by how many overlapping and confusable experiences occur.

Interestingly, recent evidence suggests that because the hippocampus helps us retrieve information from the past, it is also involved in imagining the future (for reviews see Addis and Schacter, [2011](#); Mullally and Maguire, [2014](#)). For example, neuroimaging studies show even more activation in the hippocampus when imagining the future than when retrieval of memories is involved (Addis et al., [2007](#)). Furthermore, patients with unilateral temporal lobectomy or hippocampal damage report fewer details when imagining potential future events (Kurczek et al., [2015](#); Lechowicz et al., [2016](#)), and neuroimaging studies show increased hippocampal activity for the initial imagining of a future event, compared to the recall of a previously constructed imagined event (Gaesser et al., [2013](#)).

What are the implications of these findings? At least some researchers have suggested that a better ability to remember the past may be associated with better abilities to plan for the future. For example, larger hippocampal volume is associated with a better ability to think about and implement plans for the future (Jung et al., [2016](#)). Why might the hippocampus play a role? The hippocampus might aid thinking about the

future in two ways. First, the richer the store of information one can access from the past, the larger the repertoire of potential responses that one can call upon to imagine how one might act in the future. Second, as we have learned, the hippocampus serves to bind together disparate pieces of information into a coherent whole. It also may be able recombine pieces of information in a novel way to problem solve and aid thought about future actions (Schacter and Addis, [2009](#)). As we mentioned earlier, Tulving ([1985](#)) remarked that memory, and, in this case, the pivotal role of the hippocampus, allows for time travel. The hippocampus appears to not only aid us in traveling back in time, but also traveling into the future.

The Role of the Prefrontal Cortex in Retrieval

Prefrontal cortex aids in retrieval by making contributions to strategic and executive aspects of memory. Prefrontal regions aid in the organization, selection, monitoring, and evaluation of processing that occurs at retrieval, similar to their role in encoding.

Deficits in retrieval in patients with prefrontal damage are more severe during free recall compared to recognition (e.g., Gershberg and Shimamura, [1995](#); Wheeler et al., [1995](#); MacPherson et al., [2016](#)). In free recall, there are minimal cues at test time to aid memory performance and a strategic search through memory must be performed. For example, if trying to answer the question “What was the name of that actor who starred in the movie La La Land?” one might need to do a strategic search through memory thinking about what this actor looks like or what other films you might have seen him in to access his name. In contrast, in tests of recognition memory, a search through memory is not required as the possibilities are already provided (“Did Justin Timberlake, Ryan Gosling, Zac Efron, or Matt Damon star in La La Land?”). Also suggesting that the prefrontal cortex is involved in organizing and monitoring memory retrieval, patients with damage to this area tend to confabulate, generating narratives that include false memories (e.g., Moscovitch, [1995](#)). In some cases, they show an overreliance on familiarity to make their decisions, instead of correctly monitoring whether a specific

item was indeed seen. This problem is reflected in an increased proportion of false positives in recognition memory tasks (saying “yes” that an item was viewed when in fact it was not) (Schacter et al., [1996](#); Curran et al., [1997](#)).

Evidence from neuroimaging indicates that regions of prefrontal cortex are reliably activated during memory retrieval. As we discussed with regards to encoding, these effects are lateralized. For example, left posterior PFC is activated by verbal tasks, including word generation, word classification, and word memorization, while right PFC is activated for nonverbal tasks such as face recognition (McDermott et al., [1999](#); Wagner et al., [1998](#)).

At least some studies suggest that activity in posterior regions of the prefrontal cortex is more related to retrieval attempt than to retrieval success (Buckner et al., [1998](#); Konishi et al., [2000](#)). That is, the amount of activation observed in this region is related to the effort required when retrieval is being attempted, and is independent of whether the item is successfully remembered. Such findings fit with the idea that prefrontal regions are involved in guiding the executive processes used to retrieve memories – the harder it is to retrieve information, the more effortful the search.

In addition to strategically aiding in memory recall, prefrontal regions may also play a role in suppressing the retrieval of memories (for review see Anderson et al., [2016](#)). It may be effectively inhibiting or down-regulating the hippocampus so as to preclude memory retrieval (Depue et al., [2007](#); Depue, [2012](#)). Researchers and clinicians alike are intrigued by such findings because they may hold the key to helping people overcome flashbacks and other intrusive memories associated with the experiencing of traumatic events. This role of the prefrontal cortex in suppressing memory retrieval appears to be part of a more general prefrontal mechanism that is involved in inhibitory control (Depue et al., [2015](#)), which we discuss in more detail in [Chapter 11](#) on executive function.

The Role of the Parietal Cortex in Retrieval

Similar to prefrontal cortex, damage to parietal regions does not lead to severe memory deficits, yet this region nonetheless contributes to memory retrieval through its role in attentional and integrative aspects of memory. Currently, the exact role that parietal cortex plays in retrieval remains unclear, but a variety of models have been proposed (see Wagner et al., [2005](#); Cabeza et al., [2008](#); Gilmore et al., [2015](#); Sestieri et al., [2017](#) for reviews). Some suggest that parietal regions play a role in helping to direct and maintain attention to internally generated information in memory that is most important for retrieval. Others argue that parietal regions help to assess familiarity of information which in turn predicts attentional capture for retrieval. Still others posit that parietal regions play a role in integrating information from different brain regions according to the strength of the memory. These models are all consistent with a more general role the parietal cortex plays in attention (as we discuss in more detail in [Chapter 10](#)) and with its role in integrating information from various modalities. During memory retrieval such operations are performed on internal representations, that is, those related to memory, rather than on stimuli from the external world. Like prefrontal cortex, the parietal cortex is performing operations on memory retrieval that it can also apply in other domains.

Now let's discuss some of the evidence regarding parietal contributions to memory retrieval. First, patients with parietal lesions show subtle deficits in memory retrieval (see Berryhill, [2012](#), for review). For example, when asked to recall information about various autobiographical memories, patients with bilateral parietal damage report information in less detail and less vividly than controls. However, when asked specific questions about their lives, they can answer without difficulty, indicating that the information was successfully retained (Berryhill et al., [2007](#)). Relatedly, patients with parietal damage have less confidence in their memory recall (Simons et al., [2010](#)) and are less likely to use retrieval cues (Ciaramelli et al., [2010](#)). Such findings suggest that parietal damage may affect the ability to integrate different components of a memory, direct attention to specific details to be retrieved, or to assess familiarity – all potential factors described above.

Neuroimaging and electrophysiological studies also suggest a role for the parietal cortex in retrieval. Neuroimaging studies report left parietal activation in memory retrieval tasks, regardless of the nature of the content (e.g., verbal, nonverbal) or the modality (e.g., auditory, visual) of the memory (see Vilberg and Rugg, [2008](#)). More specifically when recognition memory is required, left parietal cortex exhibits more activation for studied items correctly identified as “old” – that is, correctly remembered – than novel items correctly identified as “new,” regardless of the nature of the materials (Henson et al., [1999](#); Konishi et al., [2000](#); Sanders et al., [2000](#)). As discussed above, similar patterns are observed with ERPs. The old/new parietal positivity effect (refer back to [Figure 9.21](#)) is greater for previously seen than unseen items, and it too is observed regardless of whether or not an explicit memory decision is required. Finally, recent research using multi-voxel pattern analysis provided evidence that the type of information being recalled (e.g., face versus scene) is represented by parietal regions in addition to evidence that parietal activity signals that memories have been successfully recalled (Kuhl and Chun, [2014](#)). In sum, while the exact process that the parietal lobe contributes to memory retrieval remains somewhat unclear, this region is nonetheless making a contribution.

In Focus: Does Sleep Help You to Remember?

How you ever heard someone say, “I think I’ll sleep on it”? The idea that the act of sleeping might help one’s memory actually goes back to ancient times. Around the first century A.D., the Roman rhetorician Quintilian noted that “what could not be repeated at first is readily put together on the following day; and the very time which is generally thought to cause forgetfulness is found to strengthen the memory.” But is there any truth to this idea?

Recently scientists have begun to examine whether sleep might indeed play a role in enhancing memory. In fact, research results in animals and humans suggest that getting a good night’s sleep may help one to remember (see Stickgold, [2013](#);

Diekelmann and Born, [2010](#), for reviews). Research has found that both explicit/declarative and implicit/procedural memory are aided by sleep. Boosts in performance after sleep compared to wakefulness have been found for procedural tasks such as mirror tracing (Plihal and Born, [1997](#)), motor sequencing (Fischer et al., [2002](#)), and word-stem priming (Plihal and Born, [1999](#)). Also aided by sleep are tasks of associative memory, which are likely to rely on the hippocampus (Gais et al., [2006](#); Talamini et al., [2008](#)). Sleep may also aid in language learning, from acquiring words (Henderson et al., [2012](#)) to more generalizable linguistic rules, such as learning new grammatical constructs (Batterink and Paller, [2017](#); Schreiner and Rasch, [2017](#)).

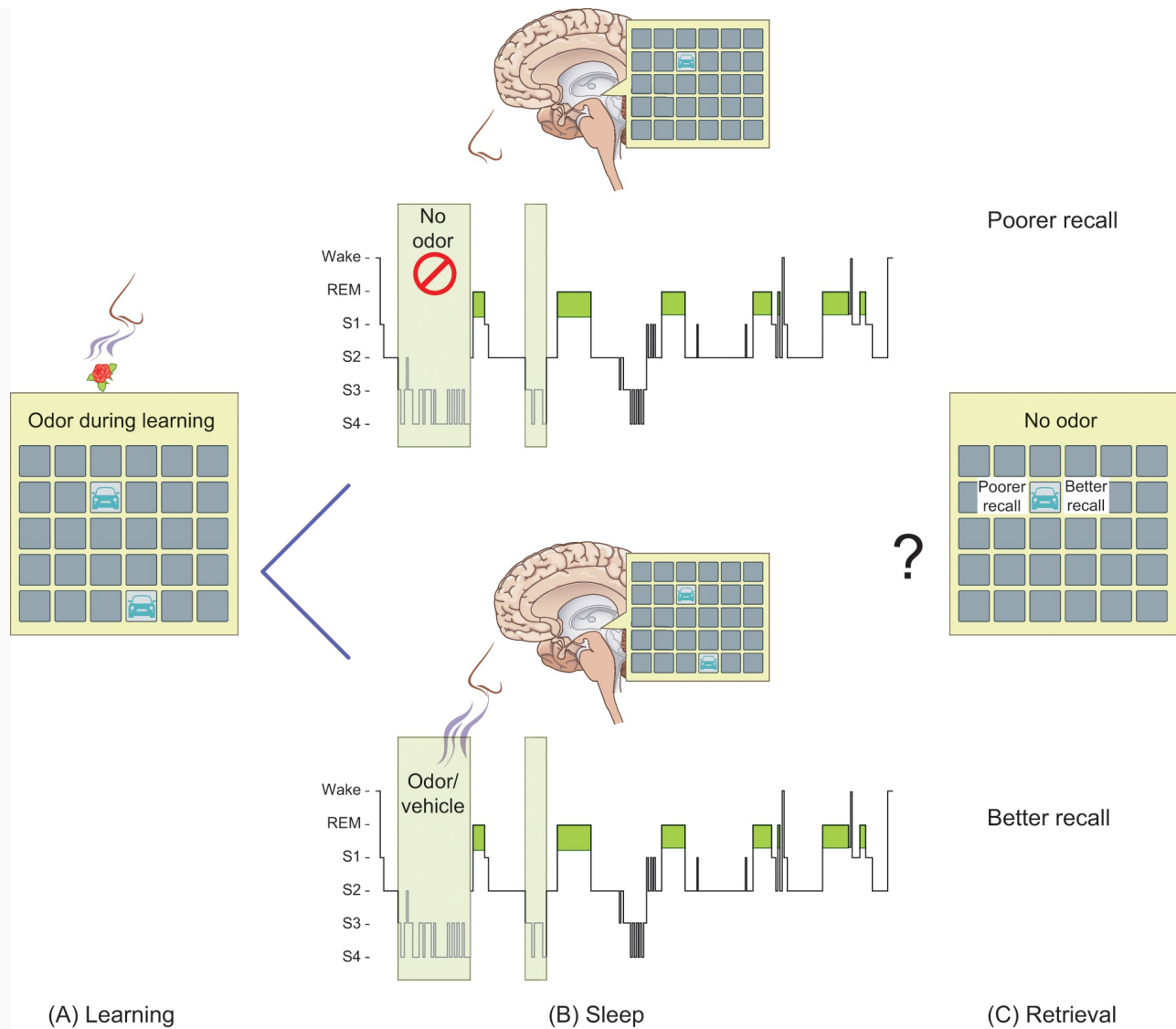
What are the potential mechanisms by which sleep might aid memory? At present there is no agreement among researchers, but a number of possibilities are being considered (see Axmacher et al., [2009](#); Ellenbogen, Payne, et al., [2006](#), for reviews). One interesting possibility is that sleep aids the consolidation process, and that such consolidation buffers old memories from interference by new ones. Evidence for this viewpoint comes from a study in which four groups of people were taught cue–target word pairs (e.g., blanket–village). Participants were given the cue and asked to recall the target. The first two groups were simply tested for their recall, one group following 12 hours of wakefulness, and the other following 12 hours of sleep. The people who were tested after sleep had marginally better recall (94%) compared to those who remained awake (82%). In the other two groups, 12 minutes before testing of the original pairs, they were taught a new target to the same cue (e.g., blanket–rubber). Typically, learning a second target to the same cue reduces recall for the first target. What was so interesting was that this effect was much increased for the group that had just had 12 hours of wakefulness (32%) versus the group that had had 12 hours of sleep (76%). This finding suggests that sleep

allows the consolidation of episodic memories, so as to become more resistant to interference by subsequent learning (Ellenbogen, Hulbert et al., [2006](#)).

One neural process that has been proposed as potentially helping to consolidate memories is the reactivation of already stored memories during the time after learning. Some interesting evidence ties such reactivation to activity in the hippocampus, neocortex, and prefrontal cortex during sleep after the learning event. For example, some researchers noted that hippocampal neurons active during an animal's exploration of the spatial parameters of an environment went on to fire at an elevated rate during subsequent sleep (Pavlides and Winson, [1989](#)). Other researchers (Wilson and McNaughton, [1994](#); Skaggs and McNaughton, [1996](#)) found that sets of hippocampal cells with a high degree of co-activity when an animal was exploring particular locations in an environment also show a high co-activity during subsequent sleep. Furthermore, multicell recordings in hippocampus and visual cortex during maze learning indicate that these two regions exhibit synchronized spiking patterns that are organized into frames, or stepwise increases in the activity of neuronal populations. Such frames may represent specific episodes or experiences. Notably, these multicell firing sequences are replayed during sleep, raising the possibility that specific events are being re-remembered (Ji and Wilson, [2007](#)).

A fascinating study with humans supports the idea that sleep affects the coordination of activity between the hippocampus and neocortex. Participants played a children's game known as concentration. In this game there is a matrix (e.g., six rows by five columns) of similarly colored cards. On the opposite side of each card is a figure. In the game, participants turn the items over in pairs and over time learn at which positions matching sets of figures are located. As such, it is an associative memory task. The participants played the game on two different days, but on both days the researchers presented participants with the scent of a rose during play. Then, on the night following each play day, the researcher waited until participants had entered slow-wave sleep. On one night

they presented the rose scent. This manipulation is known as targeted reactivation, as the rose scent is designed to target reactivation of specific memories. On the other night, they presented an inert substance instead. On the morning following each of these nights, participants were tested on their memory for the specific pair locations they had learned the prior day. Their memory following the evenings during which they had been administered the rose smell was 97%, but after administration of the inert substance it was only 86% (Rasch et al., [2007](#)). These findings are consistent with the idea that the hippocampus serves as a mechanism from which memories can be reconstructed from partial information, allowing for pattern completion, and that such a process may occur during sleep (see [Box Figure 9.1](#)).



Box Figure 9.1 The targeted reactivation paradigm that demonstrates how providing a portion of a memory during slow-wave sleep leads to improved memory recall.

(A) During the learning phase, participants learn that specific pairs of items are located in specific position on a grid. At the same time as they are learning those items, they also are exposed to a particular smell such as a rose. (B) Then during the sleep phase, researchers wait until the person reaches slow-wave sleep and then on certain days gives the same smell and on other days an inert substance is presented. (C) During the retrieval phase, which occurs the next morning, participants are tested on their memory for the items pairs. Performance is superior when, during sleep, they are given the specific scent to which they were

exposed during learning. These results suggest that during sleep memories in the hippocampus are being consolidated and strengthened.

(from Rasch et al., [2007](#))

As in animals, the mechanism for such memory improvements appears to be sharp wave-ripples of coupled activity that emanate from the hippocampus, neural activity which is thought to aid in neuronal plasticity (Buzsáki, [2015](#)). Slow-wave sleep has two states – an up state in which these ripples are sent out by the hippocampus and a down state in which the hippocampus is relatively silent. Using electroencephalography, researchers determined which of these two states the brain was in during portions of a targeted reactivation paradigm, in which cues associated with prior learning are given during sleep. Suggesting that these sharp wave-ripples are particularly important, researchers found that when cues were presented during the up state, recall of items associated with those cues was better compared to recall of items for which no cue was given during sleep. However, no such advantage was observed for memory for items associated with cues presented during the downstate (Batterink et al., [2016](#)).

What are the implications of these studies? They clearly indicate that if you want to memorize the facts about the brain that you are learning in this textbook, you should get a good night's sleep – and perhaps a nap after class might not be a bad idea, either! In fact, scientists have suggested that in certain business settings, employers might want to reconsider whether sleeping on the job can be helpful rather than a waste of time (Stickgold, [2009](#)).

Working Memory: The Ability to Hold and Manipulate Information On-Line

Prior sections of this chapter have explored the processes by which information is encoded, stored, and retrieved from long-term storage. In this section, we focus on a

more short-term aspect of memory: namely, working memory. As we noted earlier in our discussion of H.M., working memory is the ability that allows us to retain limited amounts of information for a short time while we are actively working on that information. We discuss evidence from patients who have a selective deficit in this type of memory, as well as the burgeoning evidence from other methodologies such as neuroimaging and neuromodulatory techniques such as TMS (D'Esposito and Postle, [2015](#)).

Patients with Deficits in Working Memory

As we have already discussed, although hippocampal damage impairs long-term memory, it leaves working memory intact. In contrast, there are patients who exhibit a selective impairment in verbal working memory, demonstrating a deficit in temporary maintenance in an active state of the information they are currently processing (see Shallice and Warrington, [1979](#); Vallar and Baddeley, [1984](#)). Their working memory is so compromised as to preclude immediate verbatim recall of as few as two items (e.g., two digits). The first well-recognized patient with such a disorder was a man known as K.F., who had a lesion in the left temporoparietal area, and showed a profoundly reduced capacity to hold in working memory even short strings of words or digits (Shallice and Warrington, [1970](#)). Nonetheless, he had intact long-term memory for word lists, paired associates, and the content of stories and discourse across significant delays.

The fact that a deficit in working memory does not also cause a deficit in long-term memory is in some ways surprising. Earlier theories of memory had suggested that working memory and long-term memory handled information in a strictly serial manner. Information was first held in a short-term store, which served as the gateway to the long-term store. The neuropsychological findings of a double dissociation between these syndromes indicate instead that working memory and long-term memory are systems that work somewhat in parallel. The working memory system operates to

maintain information in an active state to support on-line processing, whereas the long-term memory system works to create enduring records of experience for later use.

Deficits of working memory tend to be closely tied to individual information processing systems, occurring for a narrow domain of processing. Thus, the best-known example of a working memory deficit, as in the case of K.F., involves impairment of [auditory-verbal working memory](#), or what is currently known as the phonological store. This deficit consists of difficulty in repeating aloud and verbatim the contents of the immediately preceding verbal utterance, such as is required in the digit span task. Nevertheless, patients with working memory deficits can retain and recover basic content of a verbal utterance and can even learn word lists. Importantly, their working memory for other processing domains, such as spatial processing or arithmetic, is perfectly intact.

Some researchers have reported further specificity among verbal working memory deficits with buffers linked to different aspects of language processing – that of comprehension versus production (Caramazza et al., [1985](#)). They suggest that the [input phonological buffer](#) holds auditory-verbal information received by the listener on-line while an utterance is being parsed, whereas the [output phonological buffer](#) holds the phonological code on-line as a speaker is preparing his or her own utterance. Other patients have deficits in [visual-verbal working memory](#), which involve difficulty in the ability to hold visual-verbal information on-line during reading. Still other deficits occur in what Baddeley ([1986](#)) refers to as the [visuospatial scratch pad](#), which involves deficits in the ability to hold nonverbal visual information while performing perceptual analyses of the stimulus array. Thus, each of these deficits is tied to a very specific processing domain, leaving working memory for other processing domains intact. This pattern has been interpreted to support the idea of multiple working memory capacities, each intimately tied to the operation of specific information processing systems in the brain.

Studies with Nonhuman Animals: A Role for Prefrontal Cortex?

Somewhat at odds with what we have just discussed, classical evidence from lesion and electrophysiological recording studies in animals has specifically implicated the dorsolateral prefrontal cortex (DLPFC), rather than more posterior regions, as playing a critical role in working memory. The role of frontal cortex in a short-term form of memory has been known since 1935, when Fulton first used the spatial delayed-response task with dogs. In each trial of this task, the experimenter put food in one of several food wells in view of the animal and then covered them. After a delay interval, the animal was given the opportunity to choose one of the food wells to obtain the food reward (see [Figure 9.22](#)). Following frontal lobe damage, the animal was unable to perform this task, even with delay intervals as short as 1 second. Subsequent work by various investigators has shown that the deficit in performing such tasks does not require damage to large portions of the frontal lobes, but can instead be limited to dorsolateral prefrontal cortex (DLPFC) (see Goldman-Rakic, [1988](#)).

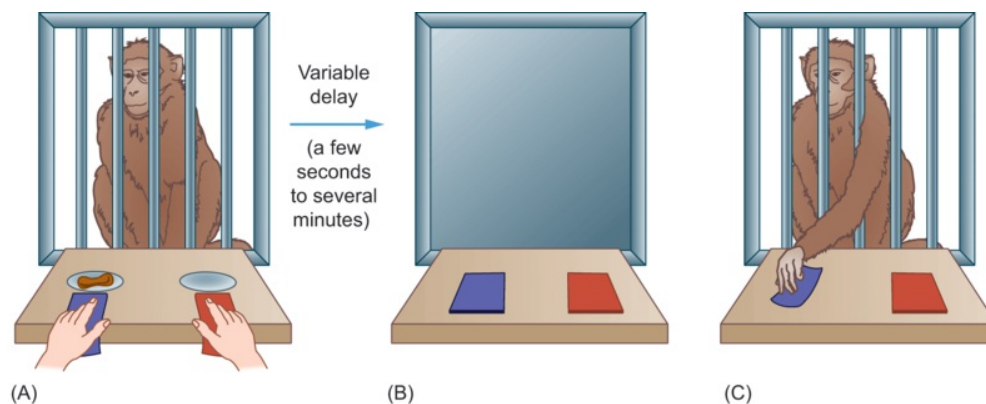


Figure 9.22 The delayed-response paradigm, used with monkeys, that illustrates the importance of dorsolateral prefrontal areas for working memory.

(A) In the cue period, the animal sees food placed under an object. (B) Then a screen drops, preventing the monkey from viewing the bowls. (C) After a delay of 1 to 10 seconds, the screen is raised and the animal gets to choose one of the two covers, obtaining the food morsel if the correct choice is made (response phase). Monkeys with dorsolateral prefrontal damage cannot perform the task when the delay is longer than 1 second.

Research with monkeys suggested a neural mechanism that might aid working memory. In classic work, Goldman-Rakic and colleagues used an oculomotor version of the delayed-response task in monkeys (e.g., see Funahashi et al., [1993](#); Goldman-Rakic, [1995](#)). In this paradigm, the monkey maintains fixation on a central spot on a display. As the monkey is doing so, one of eight possible target locations is briefly lit. Afterward, there is a short delay period during which the monkey must continue to maintain fixation. When the light at the fixation point is turned off, the monkey must move its eyes to the location where the target was presented in order to obtain its reward. During this choice period, no information in the display provides a clue as to the correct location. Rather, the monkey's response must be guided by information held in working memory during the delay period (see [Figure 9.23A](#)).

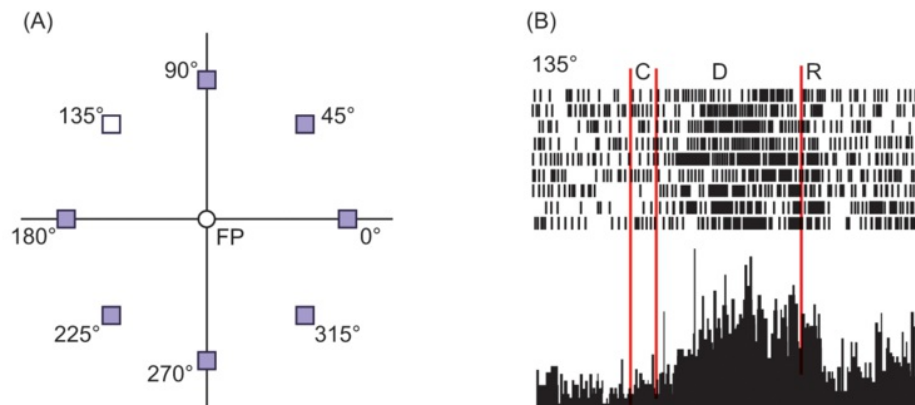


Figure 9.23 Activity in cells of dorsolateral prefrontal cortex in the monkey across a short time delay on the order of seconds.

(A) The task involves a display with a fixation point (FP) and eight possible cue locations. Whenever the light is on at fixation, the monkey's eyes must remain there. Three-quarters of a second after the onset of the light at fixation, one of the cue locations lights up for half a second. Then there is a three-second delay, after which the fixation light goes off and the monkey must respond by moving its eyes to the location at which the cue was presented. (B) A recording of activity in a neuron in DLPFC. Notice that activity increases during the delay period (D) relative to the time period of the cue (C) and the response (R). Because of this increased activity during the delay period, it has been suggested that these neurons play an important role in working memory.

Lesions to the DLPFC impair the performance of this task. The monkeys are unable to correctly guide their eye movements by memory – and the longer the delay, the greater the deficit. In contrast, eye movements guided by visual information are unaffected, indicating that the deficit is selective to memory-guided eye movements, leaving the control of eye movements in general intact.

Researchers then discovered that neurons in this region continue firing during the delay period, when the animal must maintain the position of the target in memory. These cells fire for as long as the delay period lasts, whether it be just a few or many seconds long (see [Figure 9.23B](#)). Initially this activity was interpreted to indicate that regions of the dorsolateral prefrontal cortex are actually holding information on-line during the

delay period, and therefore it represents the site of storage for information in working memory (Funahashi, [2006](#)). But as we will learn next, such an interpretation is not likely to be correct.

Insights from Neurologically Intact Individuals

If dorsolateral prefrontal cortex is the region in which information is maintained in working memory, as implied by animal models, then we would expect working memory deficits in patients with prefrontal lesions. However, patients with prefrontal damage do not have significant impairments in working memory (D'Esposito et al., [2006](#); Müller and Knight, [2006](#)). In addition, rTMS over DLPFC does not interfere with performance when individuals must do a task in which they decide if the current item is the same as the previous one (Sandrini et al., [2008](#)). If prefrontal regions do not play a special role in holding information in working memory, then where is such information held?

At least one hint is provided by the patients we discussed earlier, such as K.F., who after sustaining damage to the left temporoparietal region exhibited working memory deficits. Consistent with the idea that posterior brain regions may play a role in working memory, neuroimaging studies have revealed that posterior regions of cortex that process the specific type of item being held on-line (e.g., fusiform cortex for faces) show sustained activity across the delay period (e.g., Postle et al., [2003](#)). These results imply that when information must be retained short-term, it is reactivated in the region of posterior cortex that is storing such information.

An important but related question regards the time period during which information is active in working memory. The sustained firing of cells in prefrontal cortex was taken to suggest that information is indeed maintained in an active state across a delay, from the time it is initially noted as being as important to the time it is utilized. Another possibility is that such information is initially tagged as important, but is not maintained across the delay. Rather it is merely reactivated at that point in time when it is needed (Sreenivasan et al., [2014](#)). An intriguing recent study suggests the latter. In this task (see [Figure 9.24](#)), individuals were shown a stimulus with two items (e.g., a word above a

line segment). After an initial delay of 8 seconds, a cue came on briefly indicating for which of the two items (e.g., the top item) they should make a decision. And after 8 seconds the probe item appeared and the decision was made. Next a second cue appeared indicating whether a subsequent decision should be made about the same item (e.g., the top item) or the other one (e.g., the bottom item), and once again after 8 seconds, the probe for the second decision was shown.

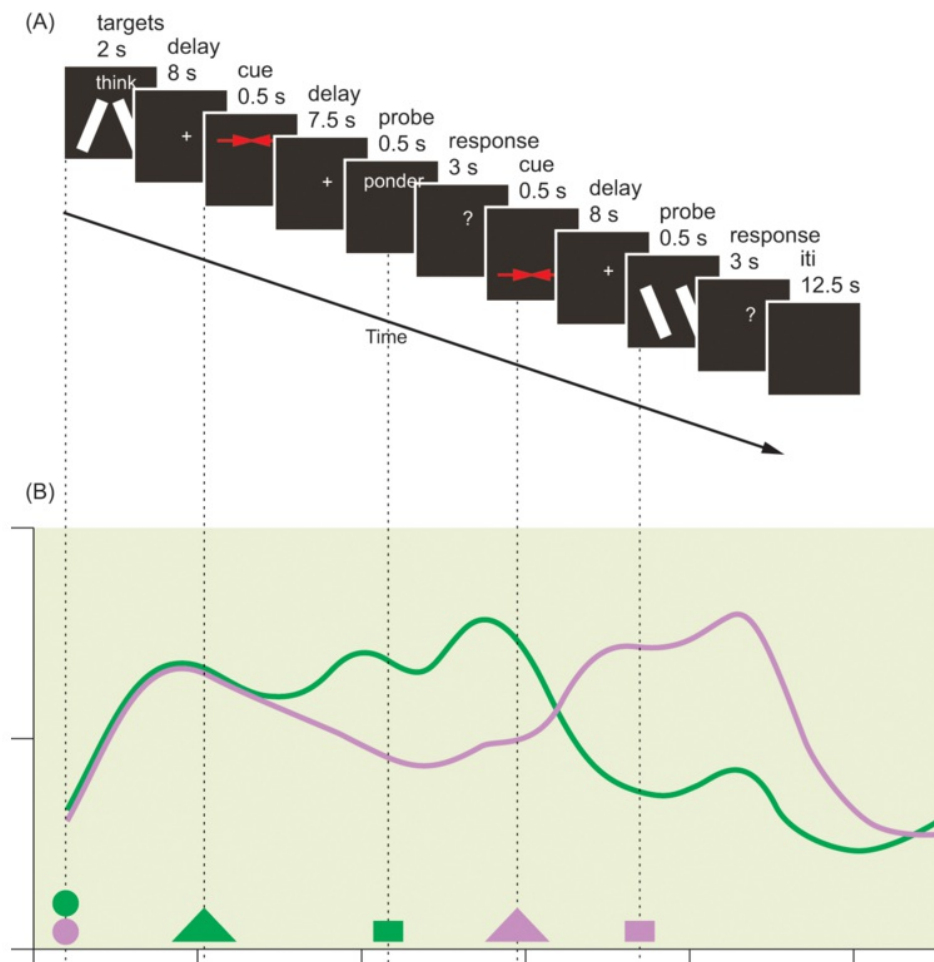


Figure 9.24 Evidence that the brain reactivates information in working memory as needed, rather than maintaining information across a delay.

(A) In this paradigm, an individual sees two items on a screen, one on top and one on the bottom. After a short delay (8 seconds), a cue appears indicating to which item (top, bottom) they should respond. After another delay, a second cue appears, which indicates whether they should respond with regards to the same item (e.g., top) or the other one (e.g., bottom). Notice that up until this point, standard theories of working

memory would argue that both items need to be retained during the delay. (B) The pattern of results showing the multi-voxel pattern of activation for each item. After the initial presentation (purple, green circles), activity for both items is observed. Then when the cue comes on, indicating on which item the decision should be made (green triangle), the activation for the cued item (green line) remains but that of the non-attended item (purple line) disappears. When the second cue (purple triangle) indicates that a decision to the previously non-attended item must be made, activity to that item (purple line) goes up and that of the other item (green line) goes down.

(from Lewis-Peacock and Postle, [2012](#))

According to the traditional animal model of working memory that says items are actively maintained across a delay, a representation of both items would need to be maintained until the point of the second cue. Consistent with those findings, prefrontal activity was observed during the delay period. However, the researchers also examined activity in brain regions, mainly in posterior cortex, that had been previously identified by multi-voxel pattern analysis as uniquely associated with each of three classes of items: words, pronounceable pseudowords, and slanted lines, respectively. They then used the multi-voxel pattern signature for a given class of item (e.g., slanted lines) as a proxy for whether a given item was being maintained across the delays.

What they observed was that prior to the first cue, multi-voxel patterns indicated activation of both attributes on that trial (e.g., words and lines). But once the cue appeared, the pattern of activity associated with the nonattended attribute disappeared, suggesting that in fact the item was not being maintained in working memory. If when the second cue appeared, a decision now needed to be made on that previously nonattended attribute, then the multi-voxel pattern for that item reappeared, and the pattern for the first item disappeared (Lewis-Peacock and Postle, [2012](#)). This study shows that it is not likely that information is maintained across a delay.

If indeed information is accessed in working memory by reactivation of representations in posterior cortex, then what role does prefrontal cortex play in

working memory? To solve this mystery, we need to turn back to psychological models of working memory. Beginning principally with Baddeley (Baddeley and Hitch, [1974](#); Repov and Baddeley, [2006](#)), some researchers have strongly advocated distinguishing storage, or maintenance, properties of working memory from control, or executive, processes of working memory. In Baddeley's model of working memory, specialized subsystems mediate the storage process, and a distinct [central executive](#) performs the mental work of controlling these slave subsystems and forming strategies for using the information they contain.

The distinction between the maintenance and manipulation portions of working memory helps to make clear at least one of the reasons that the term working memory is preferred to the term short-term memory. Working memory involves the important addition of mental "work" that is performed by the central executive above and beyond the more passive retention capability of a short-term store. Sometimes all that is demanded of working memory is the maintenance portion, such as when we have to recall verbatim the dance steps that our instructor just called out (two steps left, one step forward, one step back, two steps right). More often, though, working memory is required to do more, such as when we are preparing an ambitious meal or doing mental arithmetic.

As an example, consider the working memory challenge used in many neuroimaging studies, the N-back task, that involves both executive, or control, functions and maintenance functions. In this task, a series of items are presented one at a time and the task is to respond affirmatively when an item matches one that is N (either one, two, or three) items back. Whereas the one-back version of the task simply requires a comparison with the prior item, the two- and three-back versions require many more operations. For example, in a two-back task, with the sequence 4-2-9-2-7-5-7, the person would begin answering after the third item, with the correct responses being "no, yes, no, no, yes." Thus, on each trial of a two-back condition, a person must maintain in working memory the current item as well the last two items. But then he must compare

the current item to the earlier ones, responding affirmatively only if the current item matches the item that was shown two places back, not one or three back. After each trial, the contents of working memory must be updated to include the newest item, while the items that are more than two back must be discarded. Thus, the task requires maintaining, comparing, updating, and inhibiting, among other operations. This type of task reliably activates the prefrontal cortex (Wager and Smith, [2003](#)), and a two-back version of this task is disrupted by rTMS over prefrontal regions (Sandrini et al., [2008](#)).

Understanding that there is an executive, or information-manipulation, component of working memory helps to make sense of why working memory ends up being so dependent upon prefrontal cortex, which plays an important role in the planning, organizing, and monitoring of behavior, as we discuss in more detail in [Chapter 11](#). But in exactly what manner does prefrontal cortex organize behavior to support working memory? There is growing agreement that prefrontal cortex works to coordinate activity to access representations in posterior cortex that are needed in service of task goals, and that interactions between prefrontal and posterior regions support working memory (Eriksson et al., [2015](#)). Contrary to prior ideas, more current research using more sophisticated recording techniques from single cells suggests that it is not sustained firing but rather specific bursts of oscillations between cells in the gamma band (40–100 Hz) that support working memory. These are bursts that occur when an item is first encoded and then are reinstated when the item is retrieved after a delay (Lundqvist et al., [2016](#)).

Notice that this more current model of the neural underpinnings of working memory shares common features with the neural model of long-term episodic memory. As we learned in prior sections on long-term memory, it is not the hippocampus that stores information required for episodic memory. Rather it contains pointers to regions of posterior cortex that contain the relevant attributes of a given episode (the location, the sights, the smells, etc.). Likewise, the emerging view of working memory is that it is not prefrontal cortex that is maintaining information on-line. Rather it is coordinating

activity across posterior brain regions with regards to the attributes of information in cortical processors that are relevant to current task demands.

At this point we have considered all the major brain regions that are involved in memory processing. These include the hippocampal system (including the hippocampus and parahippocampal area), frontal lobes, left parietal cortex, amygdala, and the striatum. In [Figure 9.25](#), we synthesize this information, highlighting the critical regions and the role(s) they play in memory. To conclude the chapter, we consider the relationship between different memory systems in the brain.

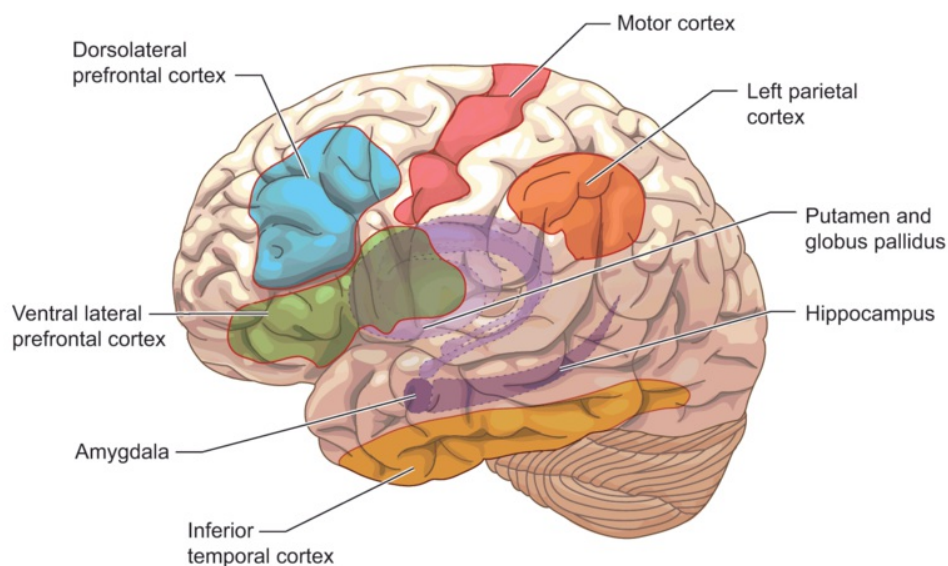


Figure 9.25 Network of structures underlying the ability to remember and learn.

Shown here are the major structures involved in memory. The hippocampal system (including the hippocampus and surrounding entorhinal cortex), shown in purple, plays a critical role in declarative and episodic memory. The amygdala, shown in deep purple, is important for emotional memory. The striatum, shown in light purple, has been implicated in procedural/implicit memory. Regions of the dorsolateral prefrontal cortex, shown in blue, are involved in working memory, whereas ventral lateral prefrontal regions, shown in green, have been implicated in encoding and retrieval. The left parietal cortex, shown in dark orange, has been suggested to play a role in retrieval. Finally, memory for perceptual information relies on sensory cortices, such as inferior temporal regions, shown in brown, whereas motor memory relies on motor regions, such as primary motor cortex, shown in red.

The Relationships Between Memory Systems

As we have just summarized, the brain has multiple different memory systems. Yet, we do not experience the different types of memories supported by these different systems as being distinct. That leads us to the questions with which we conclude this chapter. Why do we need so many memory systems in the first place, and how do such memory systems interact with one another to produce our seamless experience of memory?

Theoretical and Computational Reasons for Distinct Memory Systems

One way to understand the need for such a complicated set of neural systems to support memory is to consider what is required to remember and learn. Computational models have assumed that we need at least two types of learning systems. One system is used to generalize across different experiences via general statistical learning. Over many, many instances, general statistical features common across all experiences are extracted. For example, over many, many trips, you may have learned the best place to park your car relative to some specific locale, such as your favorite restaurant. Here your knowledge comes from many similar experiences – those surrounding similar trips to the same or similar locations in space. Because these experiences share many commonalities, the representations of them are highly overlapping. Furthermore, the learning rate of such a system is slow and incremental, as information is accumulated over many different instances.

Consider now the different requirements for a learning and memory system that is designed to help you remember where you parked your car today. Notice that the system we have just described is relatively useless for remembering such information. It only saves information about where you typically park your car. On this particular day, you may have indeed parked your car in a typical location. But maybe you got lucky and found a spot closer than usual, or, conversely, you decided to park further away so as to enjoy a longer walk in the sunshine. A system that is designed to store such information must learn quickly – on this very day you need to encode the information about where

your car is parked – and you need it to encode all the specifics of the particular place where your car is located, not just more general information about the relative neighborhood in which your car is parked. Furthermore, you need this representation to be discrete and not overlap with other representations, so that you keep the memory of where you parked your car today separate from where you parked your car yesterday and the day before and the day before that.

By now, you probably have realized that the first incremental learning system describes the type of learning that supports implicit and semantic aspects of memory; this is the type of learning that is thought to occur in specific neocortical processors, such as motor regions or visual processing areas. In contrast, the system that encodes and stores specific instances of events by combining specific different pieces of information is the type of learning that occurs in the hippocampus (O'Reilly and Norman, [2002](#); Norman, [2010](#); Kumaran et al., [2016](#)).

This perspective provides some insight into why we might have separate learning systems. The goals of these systems and how they need to store information are mutually incompatible. By having somewhat discrete and separable memory systems, our brains can retain information in more than one manner so it can be used as will best suit a particular situation.

Interacting Memory Systems for Different Types and Stages of Learning

We can now ask how these two brain systems interact. Do they act in tandem, or in opposition, or do they interact in some other manner? And does their interaction vary across different types or stages of learning? At present, relatively little definitive information exists on this issue.

Some evidence comes from fMRI studies using the weather prediction task (Poldrack and Gabrieli, [2001](#)) (refer back to [Figure 9.15](#)). As a reminder, the task involves predicting which of two outcomes (rain or shine) follows from cues presented on cards. The outcome is associated with the conjoint probabilities of the cards presented in any of a number of configurations. As noted earlier in the chapter, it is

possible to learn the task without involvement of the hippocampus, as evidenced by normal performance on this task by amnesics. However, that does not mean that in neurologically intact individuals the hippocampus plays no role in learning. In fact, at least one fMRI study suggests that the striatal- and hippocampal-dependent memory systems compete with each other over the course of learning this task. Very early on in training, activation is observed in the hippocampal system, but that activity declines across trials and in fact decreases below initial levels. In contrast, striatal activation increases across time. This pattern suggests that people at first try to utilize a strategy that relies more on declarative memory (perhaps, for example, trying to remember specific card combinations). At this point, the striatal system would not be of much use, because it learns gradually and incrementally. However, later in learning with more experience, the striatal system learns the stimulus-response contingencies, and can guide performance. Finally, the fact that the hippocampal activity decreased below baseline raises the possibility that activity in the striatal system is in opposition to that of the hippocampal system.

In another experiment, fMRI data were collected from people performing either a standard version of the weather task or a version that emphasized declarative memory in a [paired-associate learning](#) format. Whereas striatal regions were engaged by the standard version, hippocampal regions were engaged by the latter version. Furthermore, activity in one region was negatively correlated with that in the other: high activity in the striatum was associated with low activity in the hippocampus, and vice versa. The apparent competition between the learning of stimulus-response contingencies, dependent upon striatal circuits, and memory for relations, dependent on the hippocampal system, is also strongly supported by a variety of studies in rodents (Packard and McGaugh, [1996](#); Poldrack and Packard, [2003](#)).

Other studies have more directly examined the relationship between these two systems via pharmacological intervention. The advantage of such an approach is that one can examine performance in the same individuals when they are “on” the drug and when they are “off” it. These studies use midazolam, which is a sedative drug that

inactivates the hippocampus, leading to profound deficits in explicit memory. (In fact, midazolam is often given to individuals prior to invasive medical procedures, such as minor surgery, so that they can be only mildly sedated and yet have no memory of the procedure.) However, skill learning, as assessed by the mirror-reading task, is unaffected by the drug (Thomas-Antérion et al., [1999](#)). In one study, people were given midazolam, and their performance on a task thought to rely on the implicit/procedural memory system was actually superior to when they were off midazolam (Frank et al., [2006](#)). This finding suggests that the explicit/declarative learning system and the implicit/procedural systems indeed may be somewhat in competition.

These results should not be overinterpreted, however, to suggest that these two systems work in a totally antagonistic manner, such that learning in one system precludes learning in the other. Rather, as discussed earlier, each system provides a different way of storing information. It may be that the relative activation of these two systems varies by task requirements, across learning, and across individuals. As just one example, researchers gave people a task in which they had to learn the location of a single target relative to a small set of landmarks (Baumann et al., [2010](#)). Neuroimaging revealed that greater activity within the right hippocampus and the parahippocampal gyrus during the encoding of information predicted more accurate navigation in the retrieval stage, suggesting that the explicit/declarative system was important for initial learning. However, during retrieval, those people who performed better showed greater striatal activity than poor learners, suggesting that the good learners ended up performing the task via the use of a more implicit/procedural strategy. Thus, there has to be a mechanism whereby information in one system can be transferred or transformed to the other.

In sum, memory, by its very nature, is a system that allows us to relate what we have experienced in the past to what is occurring in the present. As such, memories are not static entities. Moreover, we need memories that are specific to a time and place, such as the episodes bound together by the medial temporal regions, as well as memories that fuse the present with the past, such as occurs in the statistical learning typical of skill

learning. In addition, we need memories that are independent of a context so that they can be accessed across a variety of situations, such as occurs in semantic memory. It only makes sense that there are different brain systems and processes to meet these disparate needs.

Summary

What Is Memory?

- Memory is the group of mechanisms or processes by which experience shapes us, changing our brains and our behavior.

Amnesia: A Disorder of Long-Term Memory

- Amnesia occurs after damage to the hippocampal region, or to midline diencephalic structures, such as the dorsomedial nucleus of the thalamus and the mammillary bodies of the hypothalamus.
- Anterograde amnesia is the deficit in new learning, resulting in impairment in memory of information acquired after the onset of amnesia.
- Retrograde amnesia is the impairment in memory of information that was acquired normally prior to the onset of amnesia, a deficit stretching back in time from amnesia onset.
- Amnesia occurs for information regardless of the sensory modality or the nature of the material (e.g., verbal, nonverbal), and regardless of the mode of testing, such as free as compared to cued recall.
- Amnesia selectively disrupts the process of developing new long-term memories, particularly of the relations among the elements of a scene or event, while leaving intact the ability to form short-term memories.

- Amnesics retain the ability to learn new skills and habits, and can exhibit priming, in that their performance is speeded or aided by prior exposure to the materials.
- Although amnesics exhibit a deficit in explicit tests of memory, being unable to recollect a particular study episode or learning event, they typically exhibit intact performance on implicit tests of memory, as their performance can be influenced by past experience when the learning event need not be recalled.
- Animals also exhibit memory deficits following damage to the hippocampal system, being unable to remember the relations between different aspects of an experience.
- Three characteristics of cells in the hippocampus of animals – their ability to exhibit long-term potentiation and their ability to act as place fields or to represent specific time periods – provide evidence that this brain region has attributes that enable it to play an important role in the formation of new long-term memories.

Multiple Memory Systems

- The dissociations between the affected and spared abilities in amnesia suggest that the brain contains multiple memory systems.
- One prominent viewpoint suggests that the hippocampal system is critical for explicit, conscious recall of information, whereas nonhippocampal regions support memory of an implicit, unconscious nature.
- Another prominent viewpoint suggests that the declarative memory system, which depends critically on hippocampal regions, allows one to remember the relations between the different pieces of an experience or event, whereas the procedural memory system, independent of the hippocampus, allows one to acquire and express skill through gradual incremental learning.

- Although the hippocampal system is involved in conscious recollection of a learning situation, consciousness does not rely on the hippocampus.

Nonhippocampal Regions Involved in Memory

- Memory relies in part on reactivation of those same domain-specific regions of the cortex that were activated when an event was experienced.
- Changes in patterns of activity in the domain-specific neural processors are involved in skill learning, such as motor regions involved in learning of a finger-sequencing task.
- The basal ganglia play a role in implicit/procedural learning, which usually occurs gradually and incrementally through repetition of motor, perceptual, or cognitive operations, and which leads to improved performance. The basal ganglia most likely do so by aiding in the linkage of sensory information to the motor outputs, actions, or choices required to exhibit such learning. The activity of dopaminergic cells within the basal ganglia may serve to support error-driven learning, determining whether predicted and actual outcomes are concordant or not.
- The amygdala plays an important role in fear conditioning, linking events and stimuli to a fearful experience. It also plays a role in learning stimulus–reward associations, and in the modulation of memory by emotional experiences.
- Anterior temporal regions play a role in semantic memory, which is the portion of memory that reflects our general knowledge about the world, such as facts, concepts, and categories that cut across many different contexts and are not modality- or domain-specific. In contrast, episodic memory, which is memory for a specific episode or event, appears to rely on hippocampal regions.

Brain Systems That Contribute to Encoding, Consolidation and Storage, and Retrieval

- Both the hippocampus and prefrontal regions contribute to the encoding of new memories, as activity in these regions at the time of encoding predicts subsequent memory for an item. The hippocampus binds together the different attributes of an event, whereas prefrontal regions likely aid in focusing and organizing the encoding processes.
- For at least some length of time, the hippocampus is involved in storing information or indexing where in neocortical processors discrete aspects of an event (e.g., sights, sounds, feelings) are stored.
- The index stored in the hippocampus allows memory retrieval via pattern completion of information accessed from interactions with neocortical areas.
- Prefrontal regions assist in retrieval by aiding in the search process for relevant information stored in memory, as well as selecting the most appropriate information for the current context after the relevant options have been retrieved.
- Parietal regions are implicated in recognition memory.

Working Memory

- Some patients exhibit a specific deficit in working memory while retaining their long-term memory.
- The double dissociation between these patients and amnesic patients indicates that working memory and long-term memory are supported by distinct neural systems.
- Impairments of working memory are closely tied to domain-specific processing systems, such as auditory-verbal working memory or visuospatial working memory.
- It was once thought that the continual firing pattern of neurons in dorsolateral prefrontal cortex during a delay, as observed in single-cell studies in animals,

indicated that this brain region held information on-line during a delay. However, more recent evidence from single-cell recording and analysis of multi-voxel patterns of activation in humans suggests that prefrontal regions help to select the information that is relevant for current working memory demands and points to the information in posterior cortex that needs to be activated.

- Working memory has two distinct portions: one is a buffer that maintains information on-line and is associated with retrieval from posterior brain regions; the other is important for accessing the relevant information to put into that buffer and manipulating the contents of those buffers, and is associated with the prefrontal cortex.

The Relationships Between Memory Systems

- Computational models suggest the need for two memory systems because they learn in fundamentally different manners. One of these permits generalization of knowledge through slow and incremental learning over many different instances and through the use of highly overlapping representations. The other system enables the fast learning of specific episodes and events via discrete and nonoverlapping representations.
- Evidence suggests that learning in these two systems may be somewhat incompatible and/or that they are preferentially engaged at different stages of learning.

Chapter 10

Attention



[What Is “Attention”?](#)

[Brain Structures Mediating Arousal](#)

[Brain Structures Mediating Vigilance and Sustained Attention](#)

[Selective Attention](#)

[The Time Course of Attentional Selection](#)

[Brain Regions Mediating Selective Attention](#)

[Superior Colliculus: Automatic Orienting](#)

[Thalamus: Gating of Sensory Information](#)

[Parietal Lobe](#)

[Anterior Cingulate and Supplementary Motor Area: Response-Related Selection](#)

[Lateral Prefrontal Cortex: Goal Selection](#)

[Sources and Sites of Attentional Control](#)

[Neural Mechanisms of Selection: Biased Competition](#)

[Neural Bases of Divided Attention](#)

[In Focus: Pay Attention to the Road!](#)

[Network Models of Attentional Control](#)

[A Distributed but Overlapping Network](#)

[Altering, Orienting, and Executive Attention](#)

[Selection of Goals Versus Detection of Behaviorally Relevant Stimuli](#)

The Default Network: The Lack of Attention or Internal Attention?

Hemineglect: Clinical Aspects

Clinical Features

Typical Manifestation

Not Due to Sensory Deficits

Modulated by Attentional Factors

Theories Regarding the Underlying Deficit

Treatment

Hemineglect: Implications for Understanding Brain–Behavior Relationships

Attention Based on Objects

Hemispheric Differences in Attentional Control

Processing of Unattended Stimuli

Consciousness

Summary

As he did every morning after waking, Bill went into the bathroom to begin his morning ritual. After squeezing toothpaste onto his toothbrush, he looked into the mirror and began to brush his teeth. Although he brushed the teeth on the right side of his mouth quite vigorously, for the most part he ignored those on the left side. Then he stepped into the shower and began rubbing a bar of soap to produce a frothy lather. After generously distributing the suds over the right side of his body, he began to rinse off without lathering the left side of his body.

After getting dressed, Bill went to his favorite local diner for breakfast. He ordered the daily special of two eggs, toast, bacon, and hash browns; the last two items were his favorites. When his order arrived, the waitress placed the plate in front of him with the fried eggs and the toast toward the right, and the bacon and hash browns to the left. He took one bite each of bacon and of hash browns, and then turned to the eggs and toast. Strangely, once he started eating the eggs and toast, he never took another bite of hash browns or bacon. While

Bill was sipping his coffee, a busboy, walking to the kitchen off to Bill's left, dropped a stack of dirty dishes, creating a commotion. Bill, like everyone else in the diner, watched the rattled busboy clean up the mess. Afterward, Bill resumed eating his breakfast and now heartily consumed the hash browns and bacon he had previously ignored.

When Bill asked for the check, the waitress placed it on the left side of the table. After a few minutes, he waved the waitress over and complained, saying, "I asked for my tab five minutes ago. What's taking so long?"

She looked at him quizzically, pointed to the bill on the table, and replied, "But sir, it's right here. I put it there a while ago."

With that, Bill rose to leave, and the waitress, still bemused by the whole encounter, watched him bump into the left-hand part of the door frame as he walked out into the street. As she turned to clean the table, she saw that Bill had left a generous tip. Shrugging, she said softly to herself, "I guess the customer is always right."

The seemingly bizarre behavior displayed by the gentleman in this story can be attributed to a syndrome known as [hemineglect](#) sometimes referred to as, [hemi-inattention](#). Despite having intact sensory and motor functioning, people with hemineglect ignore, or do not pay attention to, one side of space. Hemineglect is considered to be mainly a spatial phenomenon, because the neglect of information occurs with reference to a spatial frame (i.e., information contralateral to the lesion is ignored) and because all types of information, regardless of modality, on the neglected side of space are ignored. Given what you learned in [Chapter 7](#) about the important role that the parietal lobe plays in spatial processes, it should not surprise you that hemineglect often involves damage to the right parietal lobe.

Because attention is a multifaceted process that has been conceptualized in different ways, we begin this chapter by briefly discussing what attention is and how it influences

behavior. Next, we identify and discuss the many brain systems that play a role in different aspects of attention. Even more than other mental abilities we have discussed so far in this book, aspects of attention are controlled by a large and distributed network of brain structures. The first half of this chapter surveys how this network of brain structures underlies attention. The latter half of the chapter presents a detailed discussion of hemineglect. This syndrome has received much attention (no pun intended), not only because the pattern of deficits is so bizarre and intriguing, but also because it can provide further insight into how the brain is wired to help us to pay attention.

What Is “Attention”?

Attention is a concept often invoked by psychologists, but one that does not have a standard, universally accepted definition. Nonetheless, most psychologists agree that the brain has inherent limitations on the amount of information it can process at any one time. Therefore, our brains can function effectively only if there is a means to select specific information for further processing. This selective process is known as [attention](#). Just as memory is an umbrella term that covers many different types of memory, so there are also different types of attention.

[Alertness and arousal](#) represent the most basic levels of attention; without them a person is unable to extract information from the environment or to select a particular response from among alternatives. Alertness and arousal are low when you are tired or sleepy, which is why at these times you may miss important information or have trouble choosing the correct action. In some extreme cases, such as coma, alertness and arousal are so disrupted that the person is almost totally unresponsive to the outside world and has no control over his or her responses.

A closely related category of attention is [vigilance](#), which is also known as sustained attention. Vigilance is the ability to maintain alertness continuously over time. In common parlance, we often say that someone has a “short attention span” when he or

she cannot maintain consistent attention for long periods. Vigilance is important when a task must be performed in a nonstop manner – when “tuning in” and “tuning out” would be disadvantageous. Your ability to sustain attention is especially challenged whenever you try to listen to every word of a lecture for an entire class period. (And if the lecturer is particularly boring, your ability to remain alert and aroused may be taxed as well!)

A third general category of attention is [selective attention](#), which involves the selection of information essential to a task. Selective attention is often conceptualized as a filtering process that allows us to hone in on critical information from the vast amount of information available. This selection process can be performed on incoming sensory information, on information that we are keeping “in mind,” or on the set of possible responses. For example, as you read this page and try to understand what is written on it, you cannot simultaneously listen to a song on the radio and monitor the movements of people around you. Selective attention is the cognitive mechanism that allows you to select – from all the possibilities before you – the words on the page and the task of comprehension as the most salient aspects of processing that must be accomplished at this time.

A fourth general category of attention is known as [divided attention](#), which is the kind of attention that we use when we have to split our attention across tasks. In common parlance, we often refer to this ability as “multitasking.” A central concept in divided attention is that of the resource, or effort, that is required to process information. The brain is thought to have limited resources, which is why dividing our attention between tasks is difficult. Originally, these resources were thought to be undifferentiated; that is, they were assumed to be interchangeable and doled out for different tasks until none were left (e.g., Kahneman, [1973](#)). Picture a stack of US dollar bills. You can use some of them to buy breakfast, another to buy a magazine, some more to buy a bus ticket. It doesn't matter which particular bills you use for any of these purchases. However, [multiple-resource theory](#) suggests that a limited set of distinct resource pools may exist, each of which can be applied only to certain types of

processes (e.g., Wickens, [1980](#)), much as only US dollars can be spent in the United States, only euros can be spent in Europe, and only yen can be spent in Japan. For example, spatial and verbal processes appear to rely on somewhat different resources, as do auditory and visual processes, which may in part reflect the segregation of these processes in the brain. The brain's processing capacity is larger when tasks draw from different resource pools than from the same one, which is why it is easier to perform an auditory and a visual task simultaneously than to perform two visual tasks at the same time.

As you may have deduced already, attention is somewhat distinct from the other cognitive abilities we have discussed so far. It does not provide the ability to process a certain or specific type of information, such as programming a motor movement, distinguishing between different visual forms, orally producing a sentence, or remembering a name. Rather, attention serves to modulate or modify ongoing processing across all domains of function. Given this role, it should not surprise you that attentional control occurs via brain circuits that span many brain regions, as would be required to modulate processing broadly. In this section, we introduce the different neural systems that allow and enable the various types of attentional abilities discussed in the preceding section: arousal, vigilance, selective attention, and divided attention.

Brain Structures Mediating Arousal

At the most basic level, the ability to pay attention requires the nervous system to be receptive to stimulation. The brain system responsible for overall arousal is the ascending [reticular activating system \(RAS\)](#). Not surprisingly, this system is also responsible for controlling sleep-wake cycles. The RAS is so critical to alertness that coma results when it is damaged or disrupted. People in a state of [coma](#) remain with their eyes closed and are seemingly unresponsive to and unaware of the outside world. In severe cases, they may not even exhibit defensive movements to noxious or painful stimuli. Coma occurs either after bilateral lesions to the RAS or because of diffuse

problems that interfere with RAS functioning. In some instances, the factor causing coma affects the brain but not the body, as in the case of meningitis, a tumor, hemorrhage, head trauma, or seizures. In other instances, the causative factor affects other regions of the body as well, as in the case of a metabolic disorder, an abnormal gas in the blood (e.g., carbon monoxide), lack of a certain vitamin (e.g., thiamine), or the presence of a toxin (e.g., alcohol or heavy metals) (Young, [2009](#)). Coma and related states are discussed further in [Chapter 16](#).

The cell bodies of the ascending RAS are located in the brainstem and connect diffusely to most regions of the cortex, allowing it to modulate the arousal of the entire cortex. However, the ascending reticular activating system is not just one unified system but rather is composed of a number of distinct sub-branches, each of which contributes in its own way to overall arousal (Edlow et al., [2012](#)).

In general, cells in the ascending RAS connect to the cortex occur via two routes: a dorsal system that travels to the cortex via the thalamus, and a ventral route that travels to the basal forebrain and subsequently onto the cortex (see [Figure 10.1](#)). In addition to routing information to the cortex via different intermediaries, the neurons in each of these routes also rely on different neurotransmitters.

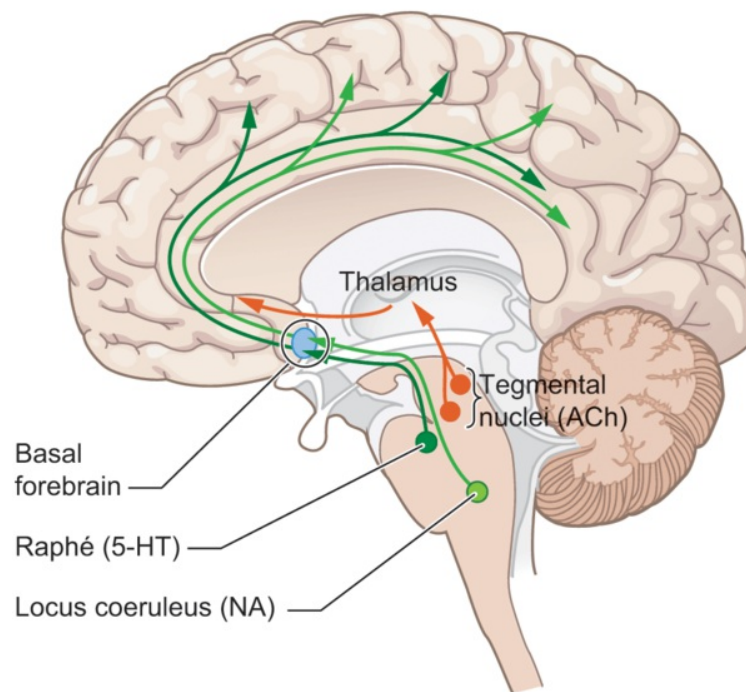


Figure 10.1 The reticular activating system is involved in overall arousal.

The reticular formation is a widespread network of neurons within the brainstem that project via one of two routes to the cortex. One route, the dorsal route, shown in orange, projects from the tegmental nuclei to the cortex via the thalamus and relies mainly on the neurotransmitter acetylcholine (ACh). The other route, the ventral route (shown in shades of green), projects to the cortex via the basal forebrain. It is composed of two separate subsystems. One, whose cell bodies are located in the dorsal raphe nucleus, mainly relies on serotonin (5-HT). The other, whose cell bodies reside in the locus coeruleus, mainly relies on noradrenaline (NA). The ascending portion of the RAS (in green) projects to many different regions of the cerebral cortex. This input serves to arouse and activate the cerebral cortex.

(from Saper et al., [2001](#))

The neurons of the dorsal system mainly rely on the transmitter, acetylcholine, and stimulation of these neurons leads to cortical activation (Jones, [2003](#)). The thalamus, to which the dorsal brainstem nuclei project, helps to keep us alert and awake by modulating the level of arousal of the cortex via glutamate, which, as we learned in [Chapter 1](#), is the main excitatory neurotransmitter in the brain. The portions of the

thalamus that are specifically implicated in this function are the [medial dorsal](#), [intralaminar](#), and [reticular nuclei](#) (see [Figure 10.2](#)). Damage restricted to these thalamic nuclei is enough to result in coma (Schiff, [2008](#)).

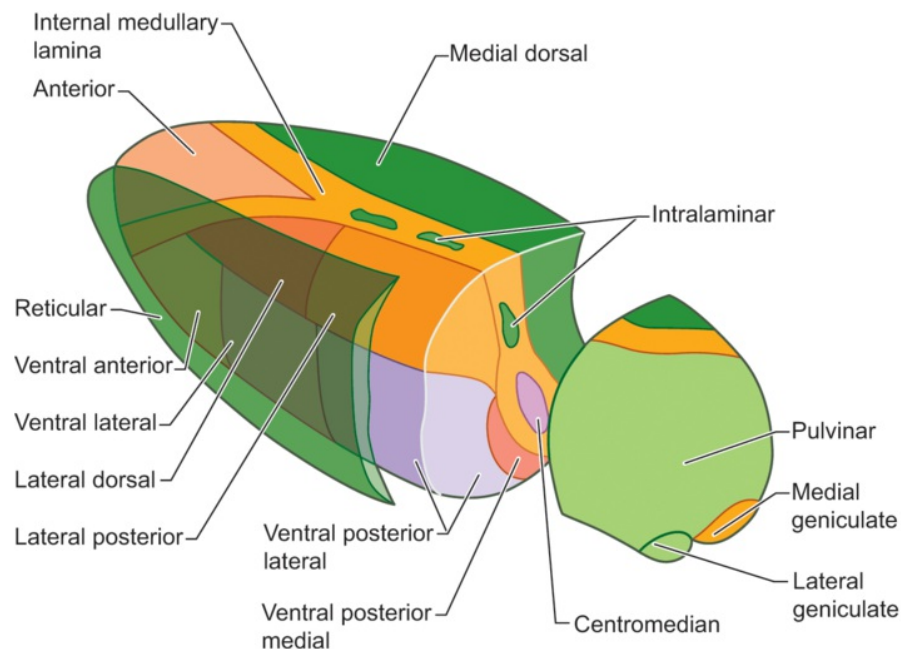


Figure 10.2 The nuclei of the thalamus thought to be involved in attention (shown in green).

The reticular, intralaminar, and medial dorsal nuclei (dark green) have been implicated in arousal and vigilance; the pulvinar and lateral geniculate (light green) have been implicated in selective attention.

A dramatic example of the role the thalamus plays in arousal is provided by a case study of a patient who had been in a [minimally conscious state](#) for six years following a traumatic brain injury. In a minimally conscious state, a person shows only intermittent evidence of awareness of the environment and the self. Researchers placed stimulating electrodes in the intralaminar nucleus and adjacent paralamina regions of the thalamus, and compared the patient's behavior when the stimulation was turned on versus when it was off. Longer periods of eye opening, increased responsiveness to commands, and the ability to control the limbs were observed when stimulation was on (Schiff et al., [2007](#)). Modulation of these same nuclei in healthy behaving monkeys leads to increases

in arousal (Baker et al., [2016](#)). Together, these pieces of evidence confirm the important role of thalamic regions in alertness and arousal.

The ventral route involves two major neurotransmitter systems: the noradrenergic system and the serotonergic system. The cell bodies of the noradrenergic system are located within the locus coeruleus of the brainstem (Berridge et al., [2012](#); Sara, [2009](#)). Single-cell recordings reveal that cells in the locus coeruleus fire at a regular slow rate (about 1 Hz), but increase their firing in response to arousing stimuli and decrease their firing during periods of drowsiness and sleep. In fact, activity in the locus coeruleus appears to prevent sleep. Moreover, lesions to this region lead to deficits in cognitive tasks in rats and monkeys, especially under conditions of high arousal or high task demand. The noradrenergic system appears to be involved in stress-related aspects of arousal and has been implicated in psychiatric disorders (see [Chapter 14](#)), such as posttraumatic stress syndrome, that are characterized by hyperaroused states (Hendrickson and Raskind, [2016](#)).

The other major neurotransmitter involved in arousal is serotonin (5-HT). The cell bodies for this subsystem are located in the raphe nucleus. This subsystem is proposed to be involved in arousal by aiding in wakefulness and suppressing rapid eye movement (REM) sleep. Activity of these cells increases during wakefulness and decreases substantially or almost ceases during REM sleep (Monti, [2011](#)). As this review illustrates, the RAS is indeed a “system” with numerous subcomponents.

Brain Structures Mediating Vigilance and Sustained Attention

Two of these neurotransmitter systems we have just discussed, the cholinergic system and the noradrenergic system, also play a role in vigilance and sustained attention. As noted, cells from the ascending reticular activating system and the brainstem cholinergic system project to the basal forebrain. Residing here are the cell bodies of another branch of the cholinergic system, which appears to play an important role in sustained

attention and vigilance. In rats, when targeted chemical lesions destroy cholinergic paths in this region, there is a loss of sustained attention (McGaughy et al., [1996](#)). Furthermore, animal studies indicate that the higher the demands in a sustained attention task, the greater the release of acetylcholine (Sarter et al., [2001](#)).

The noradrenergic system appears to be important for alerting the brain that it should get ready to receive information or make a response. For example, modulating the noradrenergic system pharmacologically in humans affects their ability to make use of a cue that provides information about the upcoming task (Coull et al., [2001](#)). Neurons from the basal forebrain and the noradrenergic system project to the midline nuclei of the thalamus, which are important for vigilance (in addition to being important for arousal, as discussed in the [preceding section](#)). For example, during a 60-minute auditory vigilance task, activity in midline thalamic regions decreased systematically with the degradation in performance over time (Paus et al., [1997](#)). The role of arousal-related regions in vigilance makes sense: to sustain a constant attentive state requires a constant, tonic level of arousal.

In fact, the thalamus may act as an interface between arousal and other aspects of attention, such as sustained attention. Evidence for this viewpoint comes from a neuroimaging study in which people had to maintain attention to detect the numeral “7” that appeared randomly in one of four positions. They performed the task under three different levels of arousal: normal levels of arousal, low levels of arousal (after sleep deprivation), and high levels of arousal (after being given caffeine). Cortical regions (discussed in subsequent sections of this chapter) showed activation during the task, but that activation did not change as a function of arousal level. In contrast, activity in ventrolateral regions of the thalamus was greatest under conditions of low arousal, when the cortex would need to be stimulated to counter the effects of sleep deprivation, and lowest under conditions of high arousal, when no such additional boost to the cortex would be required (Portas et al., [1998](#)).

Cortical regions are also involved in arousal and vigilance, and a variety of evidence converges to suggest that the right hemisphere plays a predominant role. For

example, although brain damage almost always slows responses to stimuli, damage to the right hemisphere causes the greatest decrement in performance, regardless of whether stimuli are auditory or visual (Coslett et al., [1987](#); Howes and Boller, [1975](#)) and heart-rate responses to warning signals are also disrupted by right-hemisphere damage (Yokoyama et al., [1987](#)). Converging evidence for the special role of the right hemisphere in vigilance comes from studies of brain activation in neurologically normal people. Activation in the right hemisphere is observed in vigilance tasks in which individuals must wait for a stimulus and respond rapidly (e.g., Sturm et al., [1999](#); Sturm et al., [2004](#)). The regions that become activated during vigilance tasks include frontal and inferior parietal regions of the right hemisphere as well as thalamic and brainstem regions. Moreover, electrophysiological recordings also suggest a right lateralized system for sustained attention (e.g., Arruda et al., [1999](#)). Therefore, like arousal, vigilance relies on a number of neurotransmitter systems and the thalamus. However, it also appears to involve cortical regions of the right hemisphere as well.

Selective Attention

Paying attention requires more than simply being alert and awake; we must also have a means of prioritizing certain types or pieces of information for processing over others. In fact, selective attention is probably the most intensely studied aspect of attention. Although there are many different models of selective attention, most make a distinction between what are referred to as bottom-up versus top-down aspects of attentional selection. In [bottom-up attentional selection](#), some intrinsic aspect of the stimulus itself causes it to be attended, that is, to receive priority in processing. For example, an item might grab attention because it is brighter than others or because it has emotional significance.

In contrast, in [top-down attentional selection](#), the person determines how to direct his or her attention. Attention can be directed according to any number of different features. For example, while on a hike, you could decide to direct attention to a

particular location in space, such as a point 90 degrees to your right; or you could direct your attention to particular objects, such as flowers. Furthermore, you might direct your attention based on certain physical characteristics of those flowers, such as flowers with a specific color or a particular form (e.g., variegated leaves). Alternatively, you can decide to direct attention to a particular task or goal, such as following the trail map to reach a lake. In this chapter we mainly discuss how attention is directed on the basis of physical attributes of the world (such as spatial location or color). We consider directing attention to goals and more abstract processes when we discuss executive function in [Chapter 11](#).

The Time Course of Attentional Selection

Attention does not just happen at one point in time. Rather, attention may act from the time a sensory stimulus is processed until a response to that stimulus is emitted. Keeping this idea in mind will enable you to understand why so many different brain regions are involved in selective attention: they act during different time frames of stimulus processing. Rather than thinking of attention as a single filter, it is better to think of it as a series of filters that act to enhance different aspects of information that may be relevant as the information is processed from input to output.

Although researchers now appreciate this idea, it was not always well understood that attention can act at multiple points in time. Years ago, one of the major debates that engaged psychologists studying attention was the question of exactly when attentional selection occurs. Does it occur relatively soon after the receipt of sensory information, or later? There were two schools of thought. The [early-selection viewpoint](#) suggested that attentional selection occurs at an early stage of processing, before items are identified (e.g., Broadbent, [1958](#)). The [late-selection viewpoint](#) argued that selection occurs only after sensory processing is complete and items have been identified and categorized (e.g., Deutsch and Deutsch, [1963](#)). The debate raged on, in part, because the measures of standard cognitive psychology experiments (i.e., recording accuracy and

reaction time) could not provide the critical information needed to distinguish between these two possibilities.

Event-related potential (ERP) studies, though, are perfectly suited to answer this question, because they provide information on when processes occur. ERP investigations have demonstrated that the answer to the question of when attention occurs is not an either/or proposition. Instead, attentional selection can occur both earlier and later in processing (Eimer, [2014](#)).

ERP and MEG studies indicate that at least some relatively automatic filtering or gating of sensory information occurs very soon after the receipt of a stimulus. To measure sensory gating, an auditory stimulus is presented, followed 500 ms later by the same auditory stimulus. The measure of gating is the degree to which the response is diminished on the second presentation as compared to the first (Smith et al., [1994](#)). This gating is adaptive, because the brain is registering that it has already processed the information and need not pay that much attention to it again. A diminished response to the second stimulus is reflected in an ERP component known as the P50, which occurs 35–85 ms after receipt of auditory information.

The effects of directing attention are observed a bit later, usually about 80–100 ms after stimulus presentation. Such effects are demonstrated by comparing two conditions: one in which a stimulus receives attention, and another in which the identical stimulus is presented but does not receive attention. Any difference in the ERP response to the two conditions must be attributable to the attentional manipulation. In a classic example of this type of experiment, participants are instructed to listen and count the number of target tones, such as long tones, interspersed within more frequent nontargets, such as short tones. They are told, however, to attend only to information in one ear (e.g., the left). Responses are compared for targets when they are attended (e.g., left-ear targets when attention is directed to the left ear) compared to when they are unattended (e.g., left-ear targets when attention is directed to the right ear). Researchers can obtain an estimate of when attention begins to exert its influence by noticing the point in time when the amplitude of the ERP to the attended stimulus begins to diverge from that of the

unattended stimulus. In this case, the ERP in the attended condition begins to become more negative in amplitude than that in the nonattended condition approximately 80 ms after stimulus presentation, a difference that may continue for some time (Hillyard et al., 1973). This increased negative shift for the attended stimulus is often called the N_d (negative difference) component and is shown in [Figure 10.3](#).

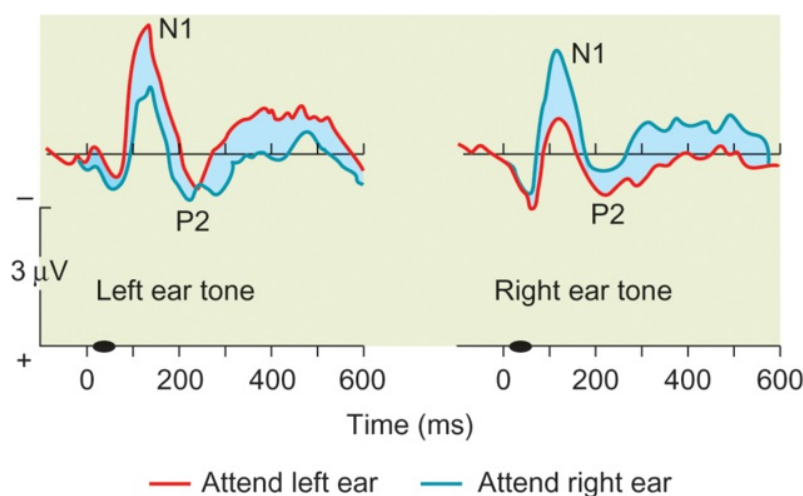


Figure 10.3 Modulation of early ERP components by attention.

The response to the stimulus is enhanced when it is presented in the attended location as compared with when it is not. (Left) For example, the amplitude of the N1 is greater to a left-ear tone when the individual is attending to the left ear (red line) than when the same tone is heard but the individual is attending to the right ear (blue line). (Right) Likewise, the response to a right-ear tone is greater when the right ear is attended (blue line) than when the left is attended (red line). The difference between these two waveforms (shaded area) is the N_d component. This effect begins relatively soon after stimulus presentation, within the first 100 ms.

Although we used auditory stimuli in this example, a similar negative electrical shift can be observed for visual and somatosensory information (Desmedt and Robertson, 1977; van Voorhis and Hillyard, 1977). These findings suggest that the early negativity in the ERP reflects a general attentional process that is not modality-specific. Because the onset of the N_d occurs as soon as 80 ms after stimulus presentation, the brain regions

and structures that direct attention can exert their influence relatively early in the stream of processing, though not immediately after receipt of information by the cortex.

Attention can act at later stages as well, as demonstrated by the effect of attentional manipulations on later ERP components. The N2pc component, which occurs approximately 180–280 ms after stimulus presentation, is thought to reflect the focusing of attention on potential target items in a display in order to prioritize processing of these items over distractors (e.g., Luck and Hillyard, [1994](#)). (It is labeled “pc” because it is recorded maximally over parietal areas contralateral to the position of the target.) The P300 (which occurs at least 300 ms post-presentation) is found only when a person is paying attention and monitoring the sensory world for a target (e.g., Donchin, [1981](#)). This component is thought to index the degree to which an attended item is task-relevant (and therefore requires an update of working memory); that is, the amount of attention paid to a task (e.g., Wickens et al., [1983](#)).

Given these findings, it should be clear that various brain regions involved in attention may not only perform different roles in the selection process, but they may also do so at different times (Luck and Kappenman, [2011](#)). That is, selection does not occur in one brain region or at one specific time. Rather, selection occurs across different portions of the brain at different times and on different time scales.

Brain Regions Mediating Selective Attention

In this section we discuss the many distinct brain regions that all work in a coordinated manner over different time frames to exert selective attention.

Superior Colliculus: Automatic Orienting

To flexibly allocate attention, you must be able to move your focus of attention from one position or object to another. The midbrain structure that has been implicated in this process, at least for visual stimuli, is the [superior colliculus](#) (refer back to [Chapters 1](#) and [5](#)). Although your focus of attention need not necessarily be the same place as where your eyes are fixed, it often is. The superior colliculus aids in shifting attention to

new locations or objects by controlling the eye movements responsible for bringing peripheral stimuli quickly into foveal vision. This process is accomplished by a [saccade](#), an eye movement in which the eyes jump from one position to the next with no processing of the intervening visual information, rather than moving smoothly across space.

Saccades come in two varieties: express saccades and regular saccades. Express saccades, which take about 120 ms, tend to be reflexive and are triggered by the appearance of a novel visual stimulus in the periphery. Research with monkeys indicates that express saccades are programmed by the superior colliculus, because when this structure is damaged, such saccades are extinguished. In contrast, regular saccades take longer, about 200 to 300 ms (Schiller et al., [1987](#)). They can be driven by the saliency of external stimuli or under voluntary control. When the frontal eye fields, which we discussed in [Chapter 4](#), are damaged, the ability to program voluntary eye movements in the absence of external stimuli is lost (Guitton et al., [1985](#)).

For example, consider a situation in which you are driving along the road on a dark and stormy night. If there is a bright flash of lightning, your superior colliculus will help automatically orient your eyes, and your attention, to its location. In contrast, your frontal eye fields will be required to voluntarily look away from that location so as to keep your eyes on the road. Generally, these structures work in tandem, with the frontal eye fields sending information to the superior colliculus to help guide the direction of eye movements. Nonetheless, when needed, the superior colliculus can also act independently to help orient the eyes automatically to salient visual stimuli.

The superior colliculus has a number of characteristics that make it well situated for aiding in attentional processing and linking them to the controlling of eye movements. The superior colliculus is divided into distinct layers. The first, the superficial layer, contains neurons that respond quickly to the onset, offset, and motion of visual stimuli, and has a retinotopic map of the contralateral side of space. As such, the superior colliculus is well suited to detect visual information that is perceptually salient with regards to its location (Shipp, [2003](#)). The other two layers, the intermediate and deep

layers, contain neurons that are sensitive both to sensory characteristics and to orienting movements. These layers are organized in an oculocentric manner with regards to where the eyes will move. These portions of the superior colliculus are tightly coupled to the oculomotor regions of the brainstem that serve as the final common pathway for control of eye movements (Wurtz and Goldberg, [1972](#)). As such, the organization of the superior colliculus allows for the quick detection of salient visual stimuli and the control of eye movements to the location of that stimulus (Krauzlis, [2014](#)).

Understanding the role of the superior colliculus in human attention has been aided by the study of patients with supranuclear palsy, which is characterized by degeneration of parts of the basal ganglia as well as specific degeneration of the superior colliculus. In everyday life, these patients often behave as if blind. Researchers have noted, “They often fail to turn towards those who approach them, to maintain eye contact during conversation, or to look at their plates when eating, even though they may still be able to do so on command” (Rafal et al., [1988](#), p. 268). In the laboratory, these patients exhibit difficulty in moving their attention from one point in space to another. Neuroimaging research confirms the role of the superior colliculus in attention: the greater is a stimulus’ ability to capture attention, the greater is the activity in this structure (Anderson and Rees, [2011](#)).

Before we leave our discussion of the superior colliculus, it is important to note that the inferior colliculus is believed to play a similar role in attention for auditory information. Nevertheless, one should not think of these regions as completely specific to the visual and auditory modalities, respectively. For example, activity of the superior colliculus is increased when attention is directed to a location that is relevant to the integration of information across modalities (e.g., the location of lips that are producing words being heard) (Fairhall and Macaluso, [2009](#)). In this manner, the superior colliculus can aid in directing attention to the location of the most salient sensory information.

Thalamus: Gating of Sensory Information

Two distinct regions of the thalamus appear to play a role in gating, or filtering, the barrage of sensory information that constantly impinges upon the brain (Saalmann and Kastner, [2014](#)). The first region is the lateral geniculate nucleus (refer back to [Figure 10.2](#)). As mentioned in Chapter 1 (see page [12](#)), information from sensory receptors is relayed to the cortex through the thalamus. The lateral geniculate is the thalamic relay point for input received from the eyes. As you may remember from [Chapter 5](#), the organization of the geniculate is such that information from each visual field projects to the contralateral portion of the lateral geniculate. In both monkeys and humans, when attention is directed to one visual field, increased activity is seen in the contralateral geniculate (McAlonan et al., [2006](#); O'Connor et al., [2002](#)). This finding suggests that attention can act early in visual processing to modulate what information will reach the cortex for further processing. In this way, the geniculate plays the role of a “gatekeeper” to the cortex, acting to enhance relevant information and suppress irrelevant information depending on the focus of attention.

The second thalamic structure involved in attention, the [pulvinar](#), plays a somewhat different role (refer back to [Figure 10.2](#)). The pulvinar appears to aid in regulating information transmission between cortical regions that are processing attentionally relevant information. In general, the pulvinar serves as the intermediary point in cortico-thalamo-cortical connections: regions of the brain that are directly connected with one another are also indirectly connected with each other via the pulvinar (Shipp, [2003](#)).

Recordings from monkeys have shown that the pulvinar synchronizes the activity between relevant brain regions involved in attentional selection (Saalmann et al., [2012](#)). In one study, monkeys viewed a cue indicating a relevant location to which attention should be directed. After a short delay, the monkeys decided whether a target item, which was surrounded by a series of irrelevant items, appeared at the cued location. Activity was recorded during the delay after the presentation of the cue but before the subsequent display to determine the effect of directing attention to that location. The pulvinar was found to be driving greater synchrony between two portions of the ventral visual stream, V4 and inferotemporal cortex that aid in object recognition. This finding

suggests that the pulvinar is helping to synchronize activity between regions that are important for detecting a potential target. This synchrony was specifically observed in the 8 to 15 Hz range, which as you may remember from Chapter 3 (see page [85](#)) is the alpha band. Later in the chapter we will discuss in more detail how synchronous alpha band activity may be a mechanism to enable attentional control across brain regions.

Pulvinar lesions generally reduce the ability to filter out distracting information. For example, when the pulvinar is chemically deactivated in monkeys, they have difficulty responding to the color of a bar at a cued location if there are other colored bars in the display (Desimone et al., [1990](#)). In humans, damage to the pulvinar interferes with the ability to engage attention to a particular location while filtering out information at other locations (Rafal and Posner, [1987](#)). Pulvinar damage also leads to difficulty in discriminating the orientation of targeted lines in the presence of distractors (Snow et al., [2009](#)). Neuroimaging studies suggest that activation of the pulvinar is specifically linked to the degree of filtering that must be done to detect a target, rather than other potential processes, such as whether the focus of attention needs to be moved to detect the target (Strumpf et al., [2013](#)).

Parietal Lobe

The parietal lobe plays two important roles in attention. First, it is involved in the overall allocation of attentional resources to a particular stimulus or task. Clinically, this is most evident in patients with right parietal lobe lesions who present with hemineglect. Not only do they ignore one side of space but overall they seem to be a bit slow or not entirely alert or oriented. We discuss evidence for this assertion later on in the chapter.

Other evidence also points to the right parietal lobe's role in allocating attentional resources. First, as discussed earlier in this chapter, right parietal regions are involved in sustained attention. Obviously, attentional resources must be allocated if one is to maintain attention across a period of time. Second, although different types of attention activate different regions of parietal cortex, common overlapping regions of activation

are found in the right intraparietal sulcus and inferior parietal cortex regardless of whether attention is directed to particular regions of space or particular periods of time (Coull and Nobre, [1998](#)) or to spatial locations or objects (e.g., Fink et al., [1997](#)). Third, damage to the temporoparietal junction, but not other regions such as the frontal lobe, eliminates the P300 (Knight et al., [1989](#)). This finding is significant because the amplitude of the P300 has been found to index the degree of attentional resources that are voluntarily allocated to a particular stimulus or task. For example, when trying to perform two tasks simultaneously, directing 80% of one's attention to Task A and only 20% to Task B will result in a larger P300 from Task A than from Task B (Kramer et al. [1985](#)). Because the P300 indexes allocation of attentional resources, and because the P300 is disrupted by damage to the temporoparietal junction, we can infer that this region is important in the allocation of attention.

More prominently perhaps, the parietal lobe plays a role in selecting information in a more precise manner after the early gating of sensory information that is performed by the thalamus. For example, when searching for an apple, information may need to be selected based on a location in space, such as when attention is directed to the location of a fruit bowl, or on the basis of an item attribute, such as the color red. Such selection appears to be carried out in three distinct manners by each of the major regions of the parietal lobe: the superior parietal lobule, the inferior parietal lobule, and the intraparietal region (see [Figure 10.4](#)).

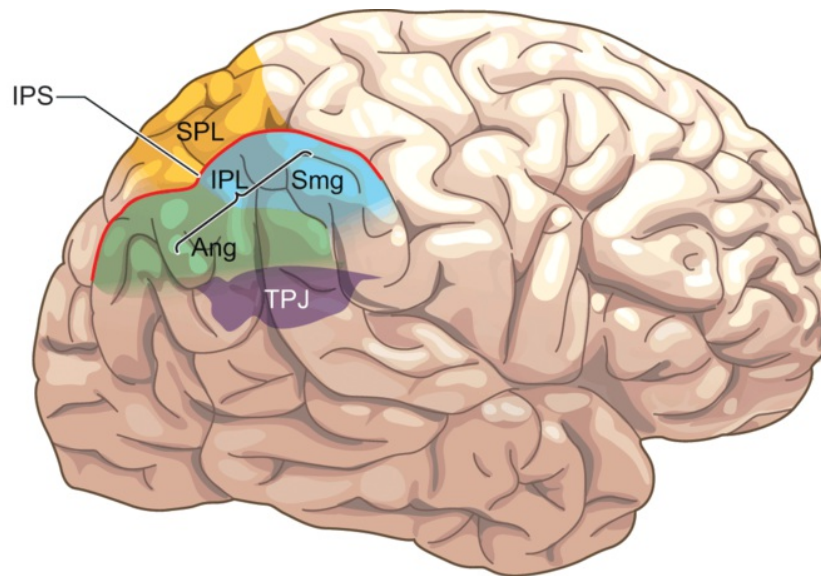


Figure 10.4 Parietal regions involved in attentional processing.

The intraparietal sulcus (IPS), shown by the red line, divides the superior parietal lobe (SPL) from the inferior parietal lobe (IPL), which is made up of the more anterior supramarginal gyrus (Smg) and the more posterior angular gyrus (Ang). Below the inferior parietal lobe is the temporal parietal junction (TPJ).

In general, the superior parietal lobule has been implicated in the top-down control of where attention will be directed and how it will be shifted (e.g., Kelley et al., [2008](#)). The inferior parietal lobe is involved in more bottom-up aspects of attentional control to help reorient attention to salient perceptual information (e.g., Corbetta et al., [2008](#)). Finally, these two streams of information are integrated in the intraparietal region, which is thought to use both sources of information to allocate weights or prioritize information to be attended (Ptak, [2012](#)).

Superior Parietal Lobe: Top-Down Selection

The superior parietal lobe is involved in what is referred to as “top-down” influences on attention, meaning that attention is directed by the person’s goals or desires rather than being driven entirely by stimuli in the environment. For example, say you are to meet your friend outside your favorite restaurant, and she tells you that she will be coming directly from a clothing store down the block. As you wait for your friend, you

direct your attention down the sidewalk to the clothing store. But then she texts you to say that she is running a little late because there was nothing of interest in that store, and instead is now picking up some items at a different store at the opposite end of the block. At this point, you need to shift your attention from one end of the block to the other. Evidence from neuroimaging studies, among other approaches, indicates that your superior parietal lobe helps you to do so (e.g., Nobre et al., [1997](#); Yantis et al., [2002](#)).

Shifting attention requires at least two steps. First, attention must be disengaged from the current location of attention and then it must be shifted to a new location, which is peripheral to the current point of fixation. Recent research suggests that the regions of the superior parietal lobe involved in disengaging attention (taking it away from fixation) may be different from those involved in shifting attention to a new location in the periphery (Kelley et al., [2008](#)). Interestingly, the superior parietal lobe appears to allow shifts of attention in general, not only shifts in attention to different spatial locations. For example, this region is also activated when one must switch attention between listening to a male voice or a female voice (Shomstein and Yantis, [2006](#)), or when one must shift between attending to a face and a house, when the pictures of each are overlapping (Serences et al., [2004](#)).

Inferior Parietal Lobe: Bottom-Up Salience

In contrast to more dorsal regions of the parietal lobe, which appear to be involved in top-down aspects of attentional control, inferior parietal regions of the right hemisphere appear to be involved in more bottom-up aspects of attention control. Support for this viewpoint comes from findings that these regions do not show an increase in activity when a cue provides information about upcoming stimuli, suggesting that they are relatively uninvolved in exerting top-down control. Moreover, portions of the supramarginal gyrus and superior temporal gyrus (often referred to as the temporoparietal junction) become very active during detection of a target when that target is at an unattended location and an individual reorients to that location. Yet, reorienting to the stimulus is not necessary to increase activity of this region, because it

also becomes active in response to infrequent changes in a stimulus stream or a feature of a stimulus regardless of the modality of that stimulus (e.g., a change from blue to red or from a sound of a croaking frog to that of running water).

Taking all these findings together, it has been hypothesized that this region is involved in detecting unattended or low-frequency events (see Corbetta et al., [2008](#)). Pointing to a role for this region in detecting stimuli, recent evidence has suggested that it is more active when one is aware of a visual stimulus compared to when that same stimulus is presented, but one is unaware of it (Webb et al., [2016](#)). Given this finding, it should not surprise you that lesions to the inferior parietal region are associated with hemineglect (Vallar and Perani, [1986](#)). When patients with hemineglect are oriented to the contralateral side of space by a cue (i.e., when top-down information is provided), they are able to detect stimuli on their neglected side. However, if no cue is provided, they do not detect the stimulus (Posner et al., [1984](#)), indicating a reduced sensitivity and a seeming lack of awareness of the unattended information.

Intraparietal Sulcus: Priority Maps

The intraparietal region is the place where these two streams of information are thought to be integrated. This region may help to create a priority map of spatial locations, which then can be used to guide the allocation of attention and selection of actions, such as eye movements (Ptak, [2012](#)). We will discuss the idea of a priority map in more detail below, but first some background will help to better situate and frame this idea.

Prominent theories of attention suggest that directing attention to particular points in space allows the features of an item at that location, such as its color and its shape, to be bound together. According to this viewpoint, “attention” is the glue that lets you know that a particular item is at a particular location. Feature integration theory (Treisman and Gelade, [1980](#)) posits that basic visual features, such as color (e.g., green) and form (e.g., X), are detected relatively automatically and can proceed in parallel across all locations in a display. However, we cannot know whether these features co-occur in a given item unless we direct our attention to the location where

that item is situated. Thus, attention binds those features together to form the percept of an item, such as a green X.

A classic illustration is provided by experiments in which a person must find a target item in a visual display that contains many nontargets, which you can try for yourself by looking at [Figure 10.5](#). When a target can be differentiated from all the nontarget stimuli on the basis of a simple visual attribute, the time required to find the target tends not to vary with the number of nontarget items. For instance, a target such as a red X will “pop out” of a field of nontargets, such as green Xs, no matter how many green Xs there are in the display. Similarly, a red X will pop out of a field of red Os. In such situations, processing is said to be “pre-attentive,” which means that attention need not be implemented to find the target. In contrast, the time required to find the target increases with the number of nontargets when a target item can only be distinguished on the basis of a conjunction of basic visual attributes (e.g., both shape and color). You should have found it harder to detect the red X in the right-hand panel of [Figure 10.5](#) because it was embedded among a mixture of nontargets, such as red Os (which share the same color as the target) and green Xs (which share the same shape as the target).

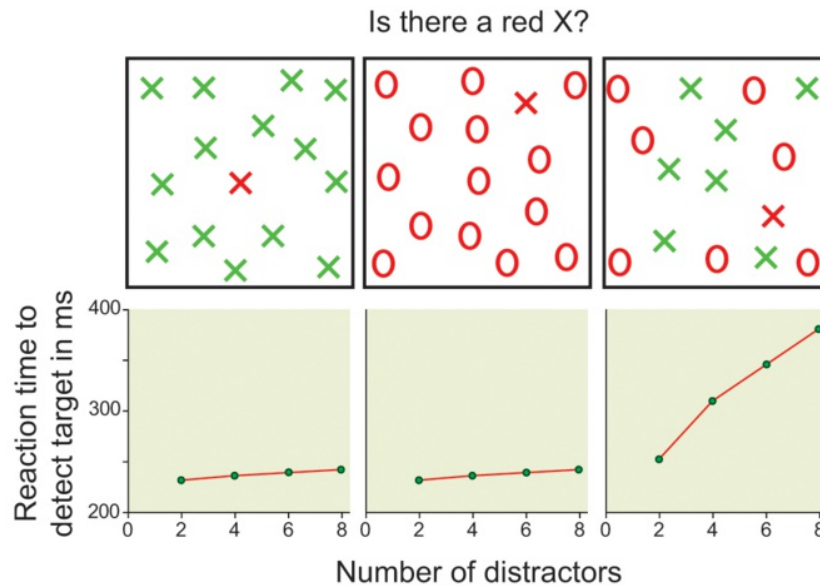


Figure 10.5 Pre-attentive versus guided visual searches.

(Top) Target detection under different conditions. (Bottom) The time taken to detect the target within the display as a function of set size. (Left and middle panels) In both cases, the target item will “pop out” of the display, because it is differentiated from the distractors on a single feature, color in the left-hand panel and form in the middle panel. As a result, the time to detect the target varies very little with an increasing number of distractors. (Righthand panel) In displays such as these, attention must be directed to different locations in space in a serial manner so as to bind together the specific features of color and form at each location until the target is detected. As such, time to detect the target increases with the number of distractors in the display.

This increase in the time necessary to detect the target occurs because attention can be directed to only one location at a time and hence must be directed serially from location to location. The more items in the display, the more locations must be sampled before the target is located. The important concept is that directing attention to a point in space allows the features at that location to be bound together so that an item can be identified (Treisman and Gelade, [1980](#)). If items are located at unattended locations, their features become “free-floating” and can be combined in illusory manners. For example, if a red X and a green O are at unattended locations, a person may report

having seen a red O, incorrectly combining one item's color with another item's shape (Treisman and Schmidt, [1982](#)).

Building on this theory, others (e.g., Wolfe, [2014](#)) have argued that information processed relatively automatically, such as color and shape, may help to prioritize where attention is directed. Some items may be more salient than others based on their basic visual characteristics – such as size, motion, orientation, and color. Such salience is stimulus-driven and is influenced by local differences among items for a given dimension. For example, a vertical line will be more salient when it is surrounded by horizontal lines compared to when it is surrounded by items that are quite similar, such as lines tilted just 10 degrees from vertical.

To understand this idea better, take a look at [Figure 10.6](#), which on the left shows the stimulus, and on the right the priority map regarding the locations to which attention could be directed. Say your task is to find a small black box in this display. Based on their basic visual characteristics, items that are large and items that are black are likely to be salient. Thus, there are higher priority values (represented in the figure by a lighter color) at those locations, which indicates bottom-up influences of stimulus salience. But top-down influences play a role as well. First, since your goal is to search for boxes based on size and color, irrelevant item attributes, such as an item's orientation or motion, provide no input to the priority map (depicted by lack of a connection to the priority map). Second, top-down influences increase the priority of locations for black items over white ones and of small boxes over large ones. As a result of both bottom-up and top-down influences, one location has a higher priority than the others and attention will be drawn to this location. Once attention is directed there, the two features regarding color and size are bound together to detect a small black box.

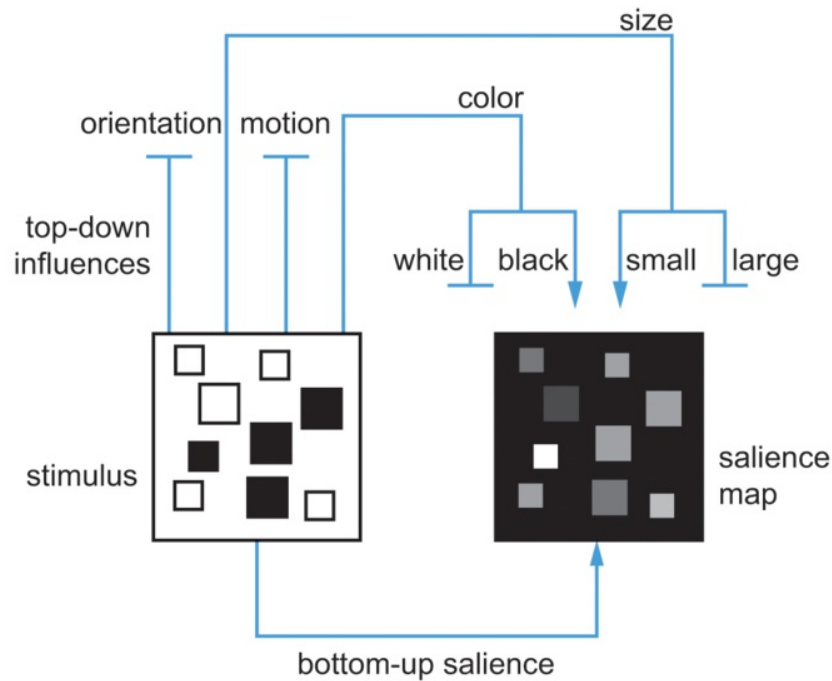


Figure 10.6 Salience maps that aid in directing attention to particular points in space, which are likely computed by the intraparietal sulcus.

(Left) A stimulus display. (Right) Salience map. Greater salience is denoted by a light color. Based on perceptual characteristics, large and dark items will be particularly salient, providing bottom-up influences on the attentional salience map. With regards to top-down influences, because the person has been told to search for a small black box, other basic stimulus dimensions will have relatively little influence (denoted by the lack of connection to the salience maps in the diagram). However, top-down influences will be important for color and shape, which define the object of interest, more specifically small items and black items. Consequently, the salience of small and black items will be increased. As a result of the conjunction of top-down and bottom-up influences, one location will be particularly salient (i.e., the location of the small black box) and will become the focus of attention.

It is thought that the intraparietal sulcus plays a major role in computing these priority maps. Consistent with this idea, firing rates of cells in the lateral intraparietal area of the monkey are influenced by both top-down and bottom-up factors (Gottlieb, 2014). Indicating a sensitivity to bottom-up factors, the cell's firing rate varies with the number of distractors, which influences the physical saliency of the target (targets are

more salient when presented with fewer distractors). Indicating a sensitivity to top-down influences, a cell's firing rate increases when a cue indicated the likely location of an upcoming target, compared to when the cue was not informative regarding the target's location (Gottlieb et al., [2009](#)). Moreover, inactivation of the intraparietal area in monkeys increases the time for detection of the conjunction of features in a visual search (Wardak et al., [2004](#)).

In humans, the intraparietal sulcus also appears to be critically involved in selecting among competing visual stimuli. This conclusion is supported by evidence from both functional neuroimaging studies and studies mapping the location of lesions in patients with attentional deficits (Vandenberghe and Gillebert, [2009](#)). Increased activation in the intraparietal sulcus is observed across a variety of tasks that involve increased visual attention, including tasks directing attention to spatial locations, those directing attention toward objects, and those involving the co-occurrence of visual attributes. However, this region is not activated by demanding tasks that do not involve selection (e.g., Wojciulik and Kanwisher, [1999](#)). In addition, bilateral damage to parietal regions disrupts the ability to bind features together. Patients with such deficits cannot detect the conjunction of features, whereas their ability to detect a single attribute remains intact (e.g., Friedman-Hill et al., [1995](#)). Moreover, transcranial magnetic stimulation (TMS) applied to the right parietal cortex of neurologically intact adults increases the time for conjunction searches but not simple feature searches (Ashbridge, Walsh, and Cowey, [1997](#)).

Once such mechanisms in the intraparietal sulcus have selected information to attend, there is then often a need to guide action toward that location or object either through a hand or arm movement, or, more commonly, through the movement of the eyes. The lateral intraparietal area is well connected with motor regions, especially the frontal eye fields, allowing the appropriate effector (e.g., the eyes) to be moved to the location or item that has been attentionally selected.

Anterior Cingulate and Supplementary Motor Area: Response-Related

Selection

Thus far, we have discussed how the brain becomes alert and aroused, how it orients toward previously unattended information, how it performs early gating of sensory information, and then how it performs more fine-grained selection of sensory information. Once the brain has accomplished all these processes, it may also be faced with the need to select among a variety of possible responses. The regions of the brain responsible for exerting response-related aspects of attentional control are in the medial prefrontal cortex, including the anterior cingulate cortex and supplementary motor area.

It has long been known that frontal regions are involved in the control of actions, as we discussed in [Chapter 4](#). Importantly, this frontal involvement also extends to the selection or prioritization of motor actions. For example, frontal lesions cause a motor neglect that exhibits itself as an inability to make motor movements toward the neglected side of space (e.g., Damasio et al., [1980](#)). Indicating that this deficit is attentional in nature, patients with such lesions display no motor paralysis that would preclude making such movements. Moreover, this deficit is distinct from the neglect of sensory information, which is typically associated with parietal lobe damage (e.g., Bisiach et al., [1990](#)).

Recent research using a variety of methods has provided a much richer understanding of the role of medial prefrontal regions in selection of action. For example, in one study, cells within rostral areas of the cingulate motor area in the monkey brain increased their firing in response to cues that signal the motor parameters of a given trial (e.g., whether to hold or release a bar in response to the target; Isomura et al., [2003](#)). Notice that the activity here is tied to the selection of a context-appropriate action. Similarly, intracranial EEG recordings in patients about to undergo surgery for epilepsy indicate that beta-wave activity in dorsal regions of the cingulate (and portions of the SMA) are altered just prior to and immediately after a response. In contrast, theta-wave activity, which is altered in other portions of the frontal regions after a response is given, remains static (Cohen et al., [2008](#)). These findings fit with results

from research with monkeys, which also suggests a role of this region in response selection.

Findings from human neuroimaging studies also support this conclusion, indicating that the anterior cingulate cortex may be particularly important when selection of the correct action is difficult or demanding. One study using variants of the Stroop task illustrates this effect. In the Stroop task, the participant identifies the color of ink in which a word is printed (e.g., blue), while ignoring the meaning of the word itself, such as conflicting color name (e.g., “red”). Because reading is so automatic, the person usually is biased to identify the color, in this case as red. Therefore, attentional control must be exerted to suppress this response and produce the correct one (e.g., “blue”).

Because many prefrontal regions become activated by this task, in one study different types of trials were created to tease out which areas are specifically sensitive to response selection. There were three possible responses: blue, green, yellow, because these were the three colors in which the words are printed. Sometimes the distracting word named one of the three response colors: blue, green, yellow. In other cases, the distracting word named a different color that is not a potential response (e.g., “purple”). And on still other trials, the word was “neutral,” naming neither a conflicting color nor a conflicting response (e.g., the word “lot” in green ink). Brain regions that are specifically engaged to handle response conflict should show greater activity on trials when the word names a conflicting response, but equal activity on the two types of trial when the word does not name a conflicting response, regardless of whether or not that word is color-related (e.g., “purple”), and would engender different types of conflict, such as conflict at a semantic level, or not (e.g., “lot”). A medial prefrontal region spanning the anterior cingulate and supplementary motor area was the only brain region that showed such a pattern (Milham et al., [2001](#)).

In another study, cingulate activity was found to increase with the difficulty of selecting a response. One condition was more difficult because the stimuli shared a salient overlapping attribute, even though they each led to a distinct response, making

response selection a bit challenging. In another condition, response selection was simpler because each stimulus was unique and could be more easily mapped to its response. More cingulate activity was observed for the former than the latter condition (Liu et al., [2006](#)) (see [Figure 10.7](#)).

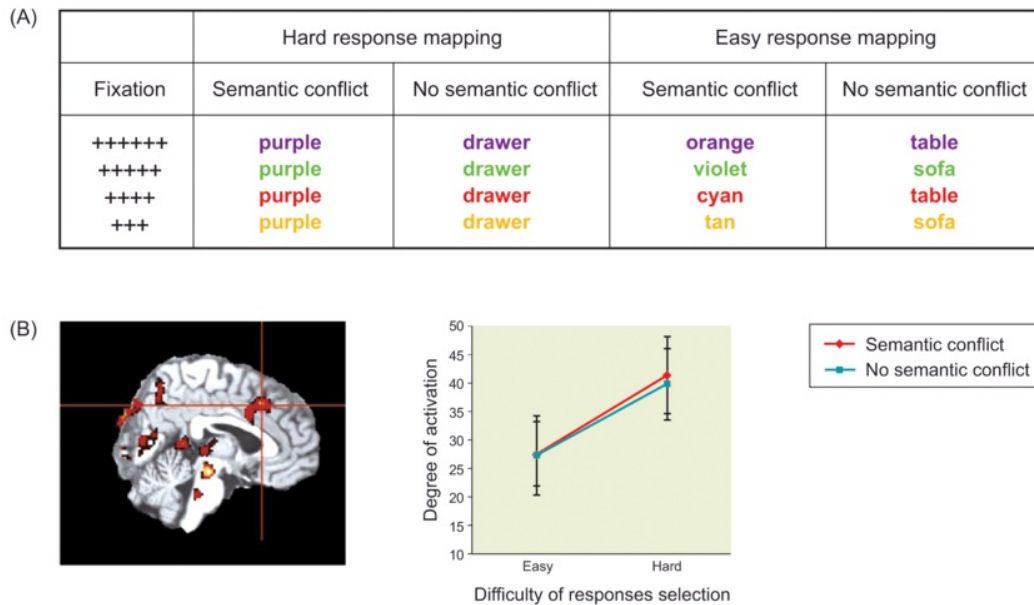


Figure 10.7 Medial regions of prefrontal cortex involved in response selection.

(A) In this experiment individuals had to indicate the color in which a word was printed. (right) In some cases, the response selection was relatively easier because the identity of the irrelevant word provided redundant information about the correct response (e.g., the word “orange” was always presented in purple ink, the word “violet” was always presented in green ink). (left) In other cases, the word did not provide redundant information, making the response selection harder (e.g., the word “purple” was shown in four different colors and hence was linked to four different responses). In addition, the researchers manipulated whether the word conflicted semantically with the ink color (e.g., the word “purple” depicted in red ink) or whether the word did not (e.g., the word “drawer” depicted in red ink). (B) This region of the anterior cingulate cortex is more active when response selection is hard (right on graph) because one stimulus is linked to four different responses, than when response selection is easier (left on graph) because each stimulus is uniquely linked to a response. Notice that this pattern is unaffected by other aspects of selection, such as whether or not the stimulus itself contains conflicting semantic information that is, whether or not it names a color.

(from Liu et al., [2006](#))

Indicating a causal role of medial frontal regions in selecting among alternative responses, TMS over this brain area increases errors only when information is present that suggests an alternative response, but not when such information is absent (Taylor et al., [2007](#)). Moreover, TMS over pre-SMA alters behavior in a variety of paradigms that involve conflicts between different types or numbers of responses (Olk et al., [2015](#)).

Our discussion so far has centered mainly on studies in which the motor response is manual, but of course actions can be made with other parts of the body as well. Other prefrontal regions play a similar role in selecting among nonmanual responses. One important region is the supplementary eye fields (see [Chapter 4](#)), which is considered the oculomotor equivalent of the SMA. Research with monkeys implicates the supplementary eye fields, in selection of the direction of gaze under conditions of response conflict (Schall and Boucher, [2007](#)). Studies from a patient with a rare lesion confined to the supplementary eye fields also suggests that this brain region is very important for selecting among competing oculomotor responses. This individual had particular difficulty in selecting the appropriate eye movements among a conflicting set of possibilities, but no such difficulty with manual equivalents (Parton et al., [2007](#)). Moreover, medial frontal regions are important for inhibiting or overriding the reflexive eye movements that are controlled by the superior colliculus (Paus et al., [1991](#)).

In sum, medial regions appear to be involved in the selection of competing responses and also when very typical or prepotent responses must be overridden, as in the Stroop task. To provide some perspective on how these mechanisms might be different from those implemented by the parietal region, consider the following situation of driving a car on a two-lane highway. The intraparietal area is likely to utilize both bottom-up mechanisms of salience to help identify the blacktop of the road in front of you (and perhaps the yellow line as well), in addition to top-down mechanisms that biases your attention to the right side of the road (assuming you are driving in the United States). This information will be fed forward to the frontal eye fields, which as we know are involved in voluntarily rather than reflexively directing the eyes to a particular point in space and also aiding in directing attention to those locations

(Wardak et al., [2006](#)). In contrast, medial regions, such as the supplementary eye fields, work to select to keep your eyes on the road in front of you in the face of salient competing responses, such as looking toward the gorgeous and salient display of autumn leaves on the trees by the roadside or toward the car passing you that is headed in the other direction.

Lateral Prefrontal Cortex: Goal Selection

As discussed in [Chapter 1](#), the prefrontal cortex plays a predominant role in processes that guide behavior. It also plays such a role in attention, setting the goal of what should be attended. Rather than selecting what stimulus should be attended or what motor response should be selected, this region guides our attention based on more abstract characteristics or goals. For example, prefrontal regions play a role in guiding the category of information to which one should attend in the Stroop task: namely, the ink color and not the meaning of the word. Because these attentional functions performed by the frontal lobe are often considered executive processes, we save most of the discussion of them for [Chapter 11](#).

Sources and Sites of Attentional Control

Here, we discuss a distinction between the roles of prefrontal versus posterior brain mechanisms in attention. One role is referred to as a source of attentional control. Regions playing this role are thought to send a signal to other brain regions, and, in so doing, bias processing toward particular information. Prefrontal regions are thought to act as a source of attentional control. In contrast, a site of attentional control is a brain region at which processing is modulated to enhance attention to a specific attribute, location, item, or other salient dimension.

To illustrate this distinction, let's consider the results from one neuroimaging study in which participants had to detect a target under two conditions (Kastner et al., [1999](#)). In one condition, they maintained attention on a central fixation point. In the other, which required greater attentional control, participants were given a cue indicating where in

the periphery they should direct their attention. In the time period after the cue but before the target, a large increase in activity was observed in frontal regions and in the superior parietal lobe. With the onset of the visual stimuli, however, little additional increase in activity was observed in these regions, regardless of whether detecting the target was demanding. Because these regions became active after the cue but before the actual display of the stimulus, they appear to serve as sources of attentional control, setting the bias for subsequent processing. However, they do not appear to be as involved when selection must actually occur, which is after onset of the visual display, because their activity was not affected by the difficulty of the actual selection process. In contrast, activity of posterior visual regions (e.g., V4) also increased after the cue, but to a much smaller degree than that of frontal and superior parietal regions. It is as if these posterior visual areas are put “on alert” by biasing signals from frontal and parietal regions. After the target appeared, however, their activity increased substantially, suggesting that these regions are actively involved in the selection process and thus acted as sites of attentional control (see [Figure 10.8](#)).

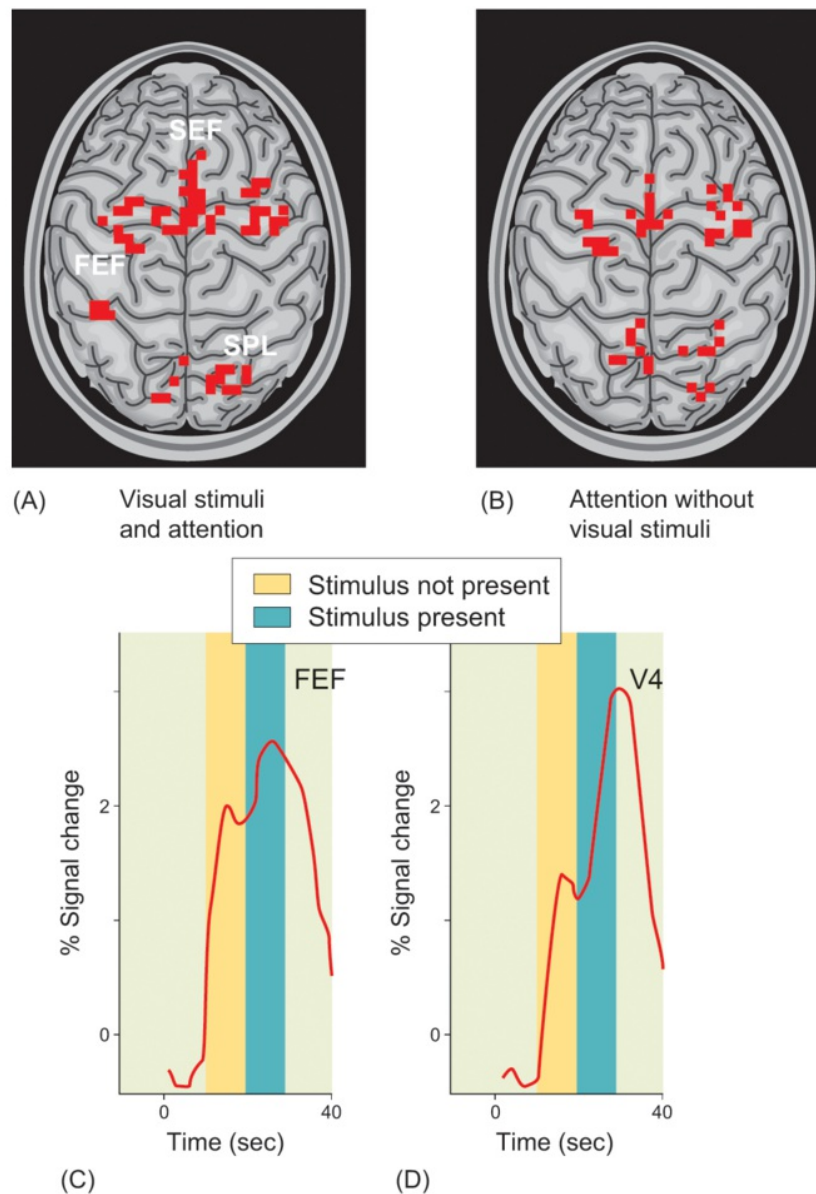


Figure 10.8 Prefrontal regions serve as a top-down source of attentional control that modulates activity in posterior brain regions.

Regions of the frontal lobe, including the supplementary eye fields (SEF) and frontal eye fields (FEF), become active when an individual is directing attention to a location – both when (A) a stimulus is present and (B) even when it is not yet present but expected. (C) Shown here is the time course of activity in the FEF as measured by fMRI. There is an increase in activity when attention is directed to the target location prior to the onset of the stimulus (yellow bar), which then increases only slightly when the stimulus actually appears (green bar). (D) In contrast, for regions in visual cortex, such as V4, there is a small increase of activity before the item appears

(yellow bar), but a substantial increase in activity once the item is present (green bar).

(from Kastner and Pinsk, [2004](#))

Now we turn our attention to consideration of processing at the sites of control. Our visual world is made up of locations in space as well as the objects that inhabit those spaces. In the past, there was a debate as to whether attention is directed on the basis of locations in space, the [space-based viewpoint of attention](#); or whether it is directed on the basis of particular objects, the [object-based viewpoint of attention](#). To make the distinction between space-based and object-based attention more concrete, let's assume that you have arranged to pick up your friend on a specific corner outside a train station. When you arrive and begin to look for your friend, you may direct your attention in a space-based manner to that particular corner and not other locations at the train station. In contrast, you may direct your attention in an object-based manner if you know that your friend will be wearing her long, oversized wool coat. As you look for your friend, you can selectively pay attention only to particular objects – long, oversized wool coats – while ignoring other objects such as ski jackets, short coats, and parkas. Studies using a cognitive neuroscience approach have provided evidence that selection can occur in a number of ways: on the basis of spatial location, on the basis of item attributes (e.g., color, form), and on the basis of whole objects. As a general overview, the site of attentional control will be the brain region specialized for processing information in the manner by which information is selected (e.g., space-based; object-based). We now discuss selection in each of these manners in turn.

Neuroimaging studies indicate that regions of visual cortex are the site at which space-based attentional effects occur. As you may remember from our discussion of the visual system, the mapping of the visual world in early visual processing areas (V1–V4) is retinotopic, so that each specific region of space is processed by a specific region of visual cortex. Of most importance for the current discussion, this mapping of visual space is inverted, so that information in one visual field is processed by the

contralateral visual cortex. Indicating that attention has space-based properties, attending to information in one visual field increases activation over extrastriate (V2–V4) regions of the opposite hemisphere (Heinze et al., [1994](#)). ERP studies indicate that this space-based attentional modulation occurs relatively early on in processing, approximately 100 ms after stimulus presentation. The amplitude of the P1 component to a visual target is enhanced when the item appears in the attended location as compared to the unattended one (Heinze et al., [1990](#)). Both PET and dipole modeling (Heinze et al., [1994](#)), as well as functional MRI (Mangun et al., [1998](#)), suggest that this component is likely generated by activity in secondary (i.e., extrastriate) visual cortex ([Figure 10.9](#)). As discussed earlier in this chapter, the parietal cortex plays a role in space-based selection by acting as the source of attentional control.

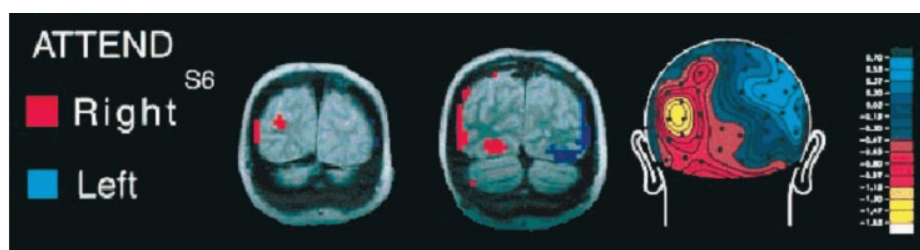


Figure 10.9 Contralateral control of spatial attention as shown by fMRI and ERPs.

The two figures on the left show activation in extrastriate cortex as measured by fMRI. Areas shown in red are those activated when the individual attended to the right side of space. Notice that activity is restricted to the left hemisphere. In contrast, the areas shown in blue are those activated when the individual attended to the left side of space. Notice that these regions are restricted to the right hemisphere. The drawing to the right shows the ERP component that occurs 100–140 ms after stimulus onset. Red and yellow indicate increased activity when attention is directed to the right side of space.

(from Mangun et al., [1998](#))

Evidence that information can be selected on the basis of item attributes or features is provided by neuroimaging studies. In one classic study, participants decided whether

two successive displays of moving colored shapes were identical or not (Corbetta et al., [1991](#)). They were told to base their decision on one of the attributes (e.g., color) and to ignore the others (e.g., speed and shape). Thus, the perceptual information was equivalent across conditions, with variations only in what attribute should be attended. When the person was attending to color, ventral visual regions sensitive to color, such as V4, were most active. When the person was attending to shape, greater activation was found in portions of the ventral visual processing stream. When the person was attending to speed, activation was greatest in area MT, the portion of the dorsal processing stream that is sensitive to motion.

ERP data had suggested that selection on the basis of stimulus attributes, such as color and shape, occurs about 250–300 ms after stimulus presentation (Anillo-Vento et al., [1998](#)), a bit later than selection on the basis of spatial features. However, more recent evidence suggests that color-based attention can act as early as 100 ms after the stimulus is presented. In these studies, participants viewed a mixed display of red and green dots in one half of the visual field, and were instructed to attend to one color (e.g., red) within that half-field. The other visual field contained an array of single-colored dots, and they were to be ignored. These dots could either be all of the attended color (e.g., red) or all of the distractor color (e.g., green). The amplitude of the P1 response was larger when the color at the unattended location was the attended color (e.g., red) as compared to when it was the distractor color (e.g., green) (Zhang and Luck, [2009](#)). Because the effects differed based on the color at the unattended location, we know that the effect cannot be due to spatially selective attention. Rather, the results reflect that the brain is biased to attend to a specific feature, regardless of where in the display that feature might occur.

Attentional selection can also be object-based (for a review, see Yantis and Serences, [2003](#)). To demonstrate object-based attention, one needs a paradigm in which the spatial location of objects is held constant, so that spatially based selection can be ruled out. Typically, paradigms used to assess object-based attention involve overlapping figures; the participant is instructed to pay attention to one object and

ignore the other. In one such study, displays included both faces and houses. When attention was directed to faces, increased activation was observed in the fusiform face area. In contrast, when attention was directed to houses, increased activation was observed in the parahippocampal place area (O'Craven et al., [1999](#)). This modulation of attention appears to occur relatively early in processing, when visual features are first recognized as forming a particular object.

As you may remember from [Chapter 6](#), a specific ERP component, the N170, is elicited specifically by faces compared to other objects. The amplitude of the equivalent magnetoencephalographic component, the M170, also reflects the effects of object-based attention. When a display contains overlapping faces and houses, the amplitude of the M170 is greater when individuals attend to faces than when they attend to houses (Downing et al., [2001](#)). Therefore, attentional selection for objects can occur as soon as 170 ms after presentation of the display.

This evidence suggests that attention can act to select information in a variety of manners: on the basis of spatial location, on the basis of item attributes, or on the basis of objects. The neural bases of these effects exhibit an interesting pattern. When selection is based on a particular characteristic, activation is increased in the brain region specialized for processing that characteristic. For example, if selection occurs on the basis of space, increased activation is observed in sensory areas that are organized with regard to space, such as early visual processing areas, and regions that provide a spatial map of the world, such as parietal regions. When attention is directed to an object, increased activation is observed in areas that process objects, such as the ventral visual processing stream. If attention is directed to a certain characteristic, such as motion, increased activation is observed in the region of the brain most sensitive to motion, MT.

Much recent research has examined the mechanisms that link processing in the sources and sites of control. Currently, it appears that one mechanism that supports selective attention is the synchronous oscillation of brain activity between the sites and sources of control. For example, in one study recordings were made both in cells in the

frontal eye fields as well as in posterior visual areas, in this case V4. There was an increase in the coupling of gamma activity (40–60 Hz) between these two regions when an attended compared to nonattended object fell within the cells' visual field. Two pieces of information suggest that it is the frontal eye fields that are driving or leading such oscillations. First, the phase of the oscillation in the frontal eye fields is about 8–13 milliseconds ahead of V4, suggesting that is the leader (Gregoriou et al., [2009](#)). Second, surgical removal of the prefrontal cortex reduces such oscillations and reduces effects of attention on neuronal processes in V4 (Gregoriou et al., [2014](#)).

Similar effects have been found in humans for object-based attention (Baldauf and Desimone, [2014](#)). In this study, people viewed overlapping faces and houses, and were told in one condition to attend to the face and in the other to attend to the house. When attending to faces, there was greater synchrony in the gamma band between prefrontal regions and the fusiform face area. In contrast, when attending to houses, greater synchrony in the gamma band was observed between prefrontal regions and the parahippocampal place area. Once again suggesting that prefrontal regions were driving the synchrony of these oscillations, the phase of activity in prefrontal regions preceded that in posterior regions by about 20 milliseconds.

Neural Mechanisms of Selection: Biased Competition

You may have noticed that we have discussed a number of general neural mechanisms that enable selective attention. One mechanism is to increase activity of those brain systems that are actively processing the information that should be attended. That can be done at the level of brain regions, as we have just discussed, at the level of patterns of activity across brain regions, such as can be detected by multi-voxel analysis (Reddy et al., [2009](#)), or at the level of single cells (e.g., Moran and Desimone, [1985](#)). Another mechanism is to increase the baseline rate of activity even before the onset of a stimulus, such as occurs in V4 in response to a cue indicating that a stimulus will

appear, as we discussed earlier. In both cases, neuron firing is modulated with regard to the attended or relevant information.

Importantly, there is another mechanism that we have not considered, which is that attention can also serve to reduce the influence of distracting information. This is well illustrated by single-cell recording in monkeys. In these studies, the scientist records the cell's response to a set of visual items, each individually when that item is the only one located within the cell's receptive field. For the sake of this example, let's say that item A makes the cell fire at a moderate rate, and item B makes it fire at a slow rate. If the cell is responding to the additive effect of all items within the receptive field (i.e., response to cell A plus response to cell B), then when both items are shown together, the firing rate of the cell should be greater than observed for either item alone. In actuality, however, when both items are within the receptive field, the cell's response is an average of the responses to each item. Thus, item B, which doesn't drive the cell's response very well, actually suppresses, or lowers, the response of the cell to item A (e.g., Reynolds et al., [1999](#)). Hence, there is competitive interaction between all task-relevant items within the receptive field. Directing spatial attention to an item's location can reduce the suppressive effects of the other items in the visual field (see [Figure 10.10](#)). Similar mechanisms have been observed in humans: directing spatial attention to a particular location eliminates the suppressive effects of other items in the visual field (Kastner et al., [1998](#)).

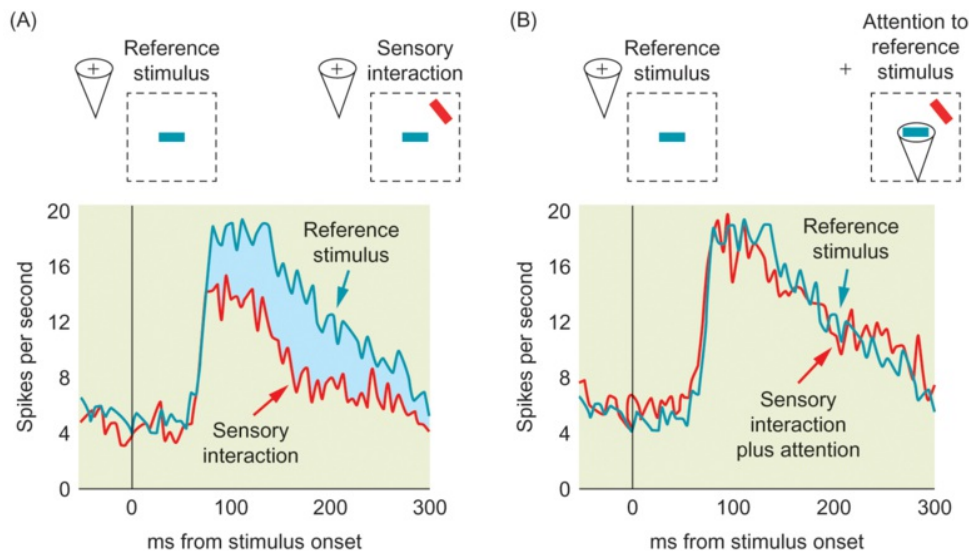


Figure 10.10 Neuronal activity that is modified by attention.

Shown here is the activity of a cell in V4 under different conditions. The cell's receptive field is indicated by the dotted square and the focus of the monkey's attention is indicated by the center of the cone (+). In all cases, the blue bar represents an effective stimulus that by itself will cause the cell to fire and the red bar indicates an ineffective stimulus that by itself will not cause the cell to fire. (A) In this case, attention is being directed to a fixation point outside of the receptive field of the cell. (Left) The reference stimulus effectively produces a robust response, but (right) when an ineffective stimulus also appears within the visual field, the activity of the cell is substantially reduced (as shown by the blue area between the curves). (B) This suppressive effect of the ineffective stimulus is negated when attention is directed at the position of the effective stimulus (right), as shown by the absence of a reduction in the cell's firing rate.

(from Pessoa et al., [2003](#))

Top-down control can also lead to inhibitory effects. For example, as compared to gamma band synchrony, which as we discussed above is associated with enhanced processes, synchronous activity in the alpha band (8–12 Hz) is thought to be important for inhibitory processing and inversely correlated with cortical excitability (Klimesch et al., [2007](#)). When attention is directed to one visual field, there is increased activity over the early visual processing regions of the contralateral hemisphere, as evidenced

by increased ERP potentials. At the same time there is increased alpha activity between prefrontal and parietal regions and early visual processing regions over the ipsilateral hemispheres, which is thought to help suppress activity in regions of the visual field that are not being attended (Doesburg et al., [2016](#)).

According to one theory (Lavie and Tsal, [1994](#); Lavie, [1995](#); Lavie and Dalton, [2014](#)), this suppressive mechanism is most likely to occur when overall attentional demands are high. When attentional demand is high, there are few resources left to process the distractors, and so they are suppressed; in contrast, when attentional demands are low, there are enough resources left over to allow for the processing of distracting information. Evidence for this viewpoint comes from a study in which people were asked to perform one of two linguistic tasks that varied in load (Rees et al., [1997](#)). In the low-load condition, participants just had to indicate whether a word was presented in uppercase. In the high-load condition, they had to determine whether the word was bisyllabic. Surrounding the central words were dots moving radially toward the edge of the screen, which induces a strong sense of movement and is known to activate area MT. These dots were to be ignored and were task-irrelevant. Researchers could use the degree of activity of area MT as an index of how much the unattended information was being processed. The researchers observed that under low-load conditions, there was increased activity in MT compared to when no motion was present, indicating that this region was processing the distracting information. More important, however, was the finding that when the processing load was high, activity in area MT was actually reduced compared to the no-motion condition. Because activity was decreased relative to a no-motion condition in which no distracting information was present, the results indicate that attention serves to suppress the processing of irrelevant information under high-load conditions.

Both the increased processing of attended information and the suppression activity for unattended information can be explained by a theory of attention known as the biased-competition model (Desimone and Duncan, [1995](#)). This model states that attention works by biasing ongoing neural activity. Such a bias can be induced in a top-

down manner by directing attention to a specific spatial location or by biasing attention toward items relevant for a task – for example, you may direct your attention toward locating a spoon rather than a fork if your goal is to eat soup. However, not all biases need be top-down. For example, a bottom-up influence that would bias the competition would be stimulus intensity – a brighter stimulus is more likely to capture attention than a dimmer one. While originally derived from research with monkeys, it is also supported by human neuroimaging studies (Beck and Kastner, [2014](#)). The idea of attention as a biasing mechanism is a powerful concept and has also been used to explain some of the deficits observed in hemineglect, as we discuss in a later portion of this chapter.

Computational models of attention have instantiated this idea of competition from both a bottom-up and a top-down perspective. For example, computational models of visual selective attention have been implemented in winner-takes-all networks. In such networks, the winner, by virtue of having the highest level of activation, stands out above the rest (i.e., distractors) and is selected for additional processing. The activation level of each unit in such models can be influenced both by perceptual salience, a bottom-up factor, and by directed spatial attention, a top-down factor (e.g., Mozer and Sitton, [1998](#)).

Similarly, competition also plays a role in top-down models of attentional control. For example, computational models of the Stroop effect argue that because word reading is so automatic relative to ink-color identification, the competition between these two processes is biased toward reading the word. Top-down control from prefrontal cortex must modify this intrinsic bias so that attention is directed to the process of ink-color identification rather than word reading (O'Reilly et al., [2012](#); Cohen et al., [1996](#)). This bias from prefrontal regions, a source of attentional control, will in turn modulate activity in posterior regions involved in processing ink color (such as V4) and word reading (such as the angular gyrus). In fact, computational models of the Stroop effect that incorporate these notions of prefrontal biasing signal

can predict patterns of activity in the brain as measured with fMRI during performance of the Stroop task (Herd et al., [2006](#)).

One interesting aspect of the biased-competition model is that it suggests that competition can be propagated across different levels of a system. For example, as a visual object gains dominance in representation within one part of a system, such as the visual cortex, it can tend to gain similar dominance in other parts of the systems (e.g., higher-order frontal and parietal areas), which then can feed back to lower levels of the system in a mutually reinforcing manner.

Evidence for this mechanism is provided by electroencephalographic studies in which conditions were compared under which faces were task-relevant or task-irrelevant. When faces were attended, increases in synchronous activity were observed across a variety of regions, ranging from posterior regions involved in face processing to frontal regions (Müsch et al., [2014](#)). Moreover, such modulation can potentially then propagate back even to the earliest parts of the visual processing stream to help tune these regions of the brain to be sensitive to specific visual features that are most likely to help discriminate and categorize the attended items (e.g., curved lines when attending to faces). As such, biased-competition in multiple sites in the brain acting simultaneously and in a mutually reinforcing manner may be an important underlying neural mechanism for attentional control.

Neural Bases of Divided Attention

Divided attention, which is required when we multitask, is the last category of attention that we consider. As discussed earlier, divided attention occurs when you must split your attention between different channels or sources of information or between different tasks. Sometimes attention must be divided between two sources of information, which can be either in the same modality or in different modalities. An example within a single modality is when you are trying to decide which movie to see with two friends, one of whom you are speaking to on the phone, and the other of whom is sitting next to you. If

they both insist on talking to you at the same time, you must try to divide your attention between the two sources of auditory information so you can comprehend what they are both saying. That can be difficult because they rely on similar resources, that is auditory processing regions of the brain.

In other cases, you may want to divide your attention across modalities, such as when you are conversing with someone while driving a car. In this case, you wish to focus your visual attention on the road while at the same time directing your auditory attention to your passenger's conversation. That may be somewhat easier because different brain regions, auditory and visual, are involved. Finally, most all psychologists agree that we cannot perform multiple tasks simultaneously due to a central bottleneck, which generally has been posited to represent a system with limited capacity, such as working memory.

Currently, there is no consensus on exactly what neural systems allow for multitasking and divided attention. Some research points to the idea that there is increased activity within prefrontal regions when attention must be divided between two tasks in different modalities (Loose et al., [2003](#); Vohn et al., [2007](#)). Studies with rTMS suggest that dorsolateral prefrontal regions may be critical. In one study, rTMS over dorsolateral prefrontal regions (but not other regions) disrupted the ability to divide attention between two simultaneously presented auditory and visual tasks (Johnson et al., [2007](#)). Moreover, some of the individuals who underwent rTMS had previously performed the divided-attention task while fMRI data were obtained (Johnson and Zatorre, [2006](#)). The more an individual recruited dorsolateral prefrontal cortex during the divided-attention condition, the more his or her performance was disrupted by rTMS over this region. Others have found the conceptual converse: improvements in performance as a result of training in multitasking are reflected in changes in activation in lateral prefrontal regions, but not in changes in sensory regions responsible for processing each task (Dux et al., [2009](#)).

This has led some researchers to argue that processing by lateral prefrontal cortex acts as a central bottleneck in resources which in some cases precludes the ability to

perform two tasks simultaneously (Dux et al., [2006](#); Szameitat et al., [2016](#)). Such a central bottleneck might represent limitations in working memory capacity or in the ability to simultaneously exert executive control over multiple tasks simultaneously. As lateral prefrontal regions play a prominent role in working memory, as we learned in [Chapter 9](#), and in executive control, as we discuss, in the [next chapter](#), such a suggestion is quite reasonable.

However, other researchers have argued that the engagement of prefrontal regions comes not because attention is divided per se, but rather because the overall demands on the brain are greater under divided compared to single-task conditions. In this account, lateral prefrontal regions are required to provide top-down control or guide how attentional resources are distributed between tasks. To examine this hypothesis, they compared a single-task condition that was matched for task difficulty with the dual-task condition. Under such conditions, the neural systems activated, including prefrontal cortex, were highly overlapping, regardless of whether participants were dividing attention between two visual tasks (Nebel et al., [2005](#)) or dividing attention between two dimensions of a stimulus (Hahn et al., [2008](#)).

This leads to the possibility that the degree to which tasks can be performed concurrently is not due to a single central bottleneck in lateral prefrontal cortex, but rather depends on the overall degree to which two tasks require use of the same brain regions for the two tasks to be performed. Neuroimaging evidence suggests that, in general, the more two tasks require similar brain regions and the more component processes they share, the more difficult they are to perform simultaneously (Nijboer et al., [2014](#); Salo et al., [2015](#)). Some intriguing research suggests that people who are less prone to dual-task interference are better at reorganizing brain networks under dual-task conditions. They appear to flexibly modify each of the single-task networks under dual-task condition so as to reduce overlap (Alavash et al., [2015](#); Alavash et al., [2016](#)). At this point, exactly how the brain allows us to perform two tasks at once, and the degree to which that is truly possible, remains an open question.

In Focus: Pay Attention to the Road!

Although we often do not think about it, driving a car requires a good degree of attentional ability. That demand is reflected in phrases that a passenger may say to a driver, such as “Pay attention to the road!” This phrase may mean that the driver is not being alert and vigilant, such as might occur during a late-night drive after too few hours of sleep and no cups of coffee. Or, the driver may not be focusing attention in the correct spatial location; for example, he may be paying more attention to the scenery alongside the road or to the back seat of the car where the children are fighting. The driver may not be focusing enough attention on the task of driving in comparison to some other task, such as eating a sandwich or reading directions. Driving requires many of the different aspects of attention we have discussed – vigilance and sustained attention, selective attention, and divided attention.

The concept of divided attention is highly relevant to a current debate about the use of cell phones while driving, both in the United States and elsewhere. Various regulations, or the absence thereof, across states and countries reflect the current lack of consensus about the safety of using cell phones while driving. In general, many people tend to think that speaking on a cell phone while driving is relatively benign. However, research in driving simulators indicates that people who talk on a cell phone while driving show as much impairment, as measured by decrement in braking speed and frequency of traffic accidents, as people who are legally drunk. Furthermore, this pattern occurs regardless of whether the driver is using a handheld or hands-free phone (Strayer et al., [2006](#)). And a review across simulated, real-life, and epidemiological studies comes to a similar conclusion (Ishigami and Klein, [2009](#)). This finding may surprise you, given that many states and municipalities within the United States have adopted a ban on handheld but not hands-free cell phone usage.

Interestingly, people seem to know that using a cell phone while driving can be hazardous, and they support laws to restrict this practice. However, people generally feel that while other people can't effectively drive when using a cell phone, they themselves are capable of doing so (Sanbonmatsu et al., [2016](#)). This is at odds with the empirical evidence that only about 2.5% of individuals are "supertaskers" who can effectively perform two tasks at once with no decrement from single-task performance (Watson and Strayer, [2010](#)).

One reason for this overly optimistic assessment of one's driving ability is likely that when people are engaged with their cell phone, they "miss" or fail to detect the errors in driving, leading to the false self-evaluation that they are driving safely. In fact, one study showed that while phone-free, drivers in a simulator could realistically assess the number of driving errors they made and the severity of those errors. In contrast, while speaking on a hands-free cell phone, the more serious the errors a person made in driving, such as failing to stop at a red light or drifting into an oncoming lane, the less likely they were to say that they had driven poorly. And ratings of performance for minor driving errors, such as failing to signal a turn, were uncorrelated with actual performance (Sanbonmatsu et al., [2016](#)).

A few studies have used brain imaging to provide insights into why such situations are so demanding by examining patterns of brain activity associated with concurrent driving and other activities. In one study, participants performed a simulated driving task, either undisturbed or while listening to spoken sentences, while fMRI was used to measure brain activation (Just et al., [2008](#)). Performance deteriorated under the dual-task condition, even though driving is mainly a visual task and comprehending sentences is an auditory task. Moreover, activity in regions of the parietal lobe involved in visual attention decreased by 37% when participants concurrently listened to a sentence compared to when they did not!

Providing insights into timing of such effects is an MEG study in which participants had to respond to a red light presented unpredictably to the left or below a driving video, either while responding to nonemotional questions, such as “What is your birthdate?” or to no questions at all (Bowyer et al., [2009](#)). Under the single-task driving condition, the degree of MEG activity over right parietal regions that was observed 200–300 ms after presentation of the red light predicted reaction times. This finding suggests that aspects of visuospatial attention predict performance. Under the dual-task conditions, the amplitude of this component was substantially reduced and reaction time increased. This finding clearly points out the degree to which the resources that could be directed to visual attention are limited by a concurrent conversation and how that results in decrements of performance under dual-task conditions.

Yet alterations in brain activation while driving and doing some other task are not limited to posterior brain regions. In a similar fMRI study, individuals either just had to drive, or else to answer “yes/no” to relatively simple auditorily presented questions (“Does a triangle have four sides?”) while driving (Schweizer et al., [2013](#)). Once again, under the dual-task condition activity in regions involved in visual attention decreased. Notably, however, activity increased substantially over lateral prefrontal regions, which as we discussed earlier in the chapter, have been proposed by some researchers to serve as a central bottleneck limiting the ability to perform two tasks at once. Thus, driving and being engaged in an interaction language-based task (such as answering questions or holding a conversation) is likely to require a certain level of executive control (even if we may not be aware of it).

Interestingly, “supertaskers” who can perform two tasks at once without decrement compared to single-task conditions do not show increased activation in prefrontal regions that most people need to engage under dual-task conditions (Medeiros-Ward et al., [2014](#)). So perhaps, they are indeed the select few who

can really drive and use a cell phone without worry! But for the rest of us mere mortals, both psychology and cognitive neuroscience suggest that public opinion is correct – it is prudent to have restrictions on using a cell phone (and other such technologies such as speech-to-text interfaced e-mail; Strayer et al., [2015](#)) while driving.

Network Models of Attentional Control

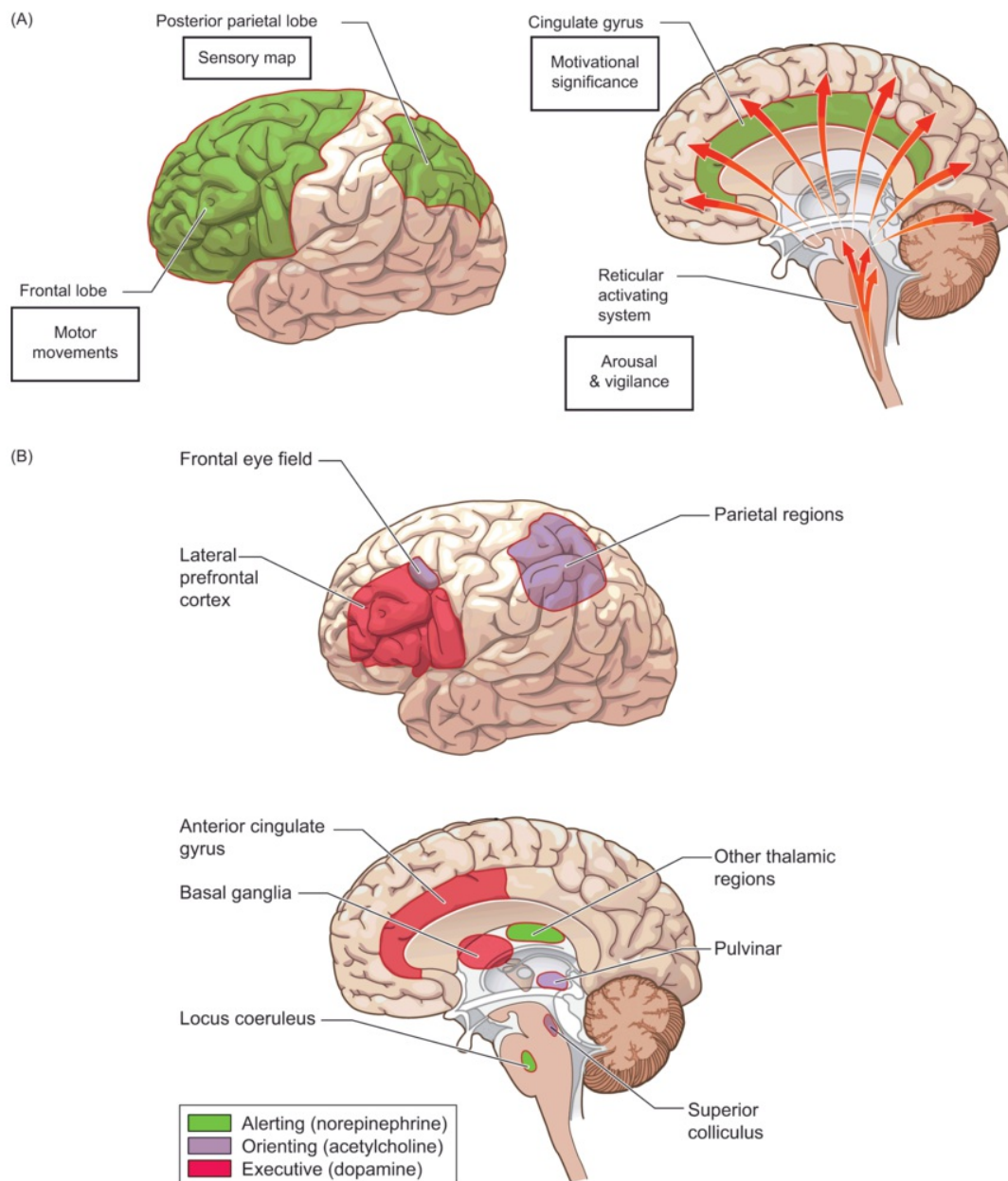
As we have seen, attentional control involves multiple brain regions and their interaction. To help understand the complexity of the neural systems underlying attention, scholars have created theoretical models to help organize our understanding of the neural bases of attention. These models provide a way to conceptualize how various regions might interact and coordinate their processing to allow for attentional control. Here we briefly introduce three models of attentional control that group the structures we have discussed so far into different subsets or subsystems.

A Distributed but Overlapping Network

One classic model of the neural systems underlying attention, proposed by Mesulam ([1981](#)), was guided by the pattern of difficulties in attentional control that result from damage to specific brain regions. This model views directed attention as being controlled by a diffuse cortical network that is simultaneously specialized and redundant. In this model, each region in the network has some specialization because the role it plays is not exactly like that of any other. However, this specialization is not absolute, in that lesions to different areas of the network can have similar effects. Thus, this model takes neither a strict localizationist approach nor one of mass action.

According to this model, each of four major brain regions plays a prominent, but not necessarily exclusive, role in controlling a certain aspect of attention. The main role of the reticular activating system is to maintain vigilance and arousal; the main role of the cingulate cortex is to impart motivational significance to information; the main role of

the posterior parietal region is to provide a sensory map of the world so as to help direct attention to particular locations or objects; and the main role of frontal regions is to provide the motor programs for moving the attentional focus around the world by exploring, scanning, reaching, and fixating ([Figure 10.11A](#)). This network requires at least three complementary and interacting representations of extrapersonal space: a sensory representation in posterior parietal cortex, a schema for distributing exploratory movements in frontal cortex, and a motivational map in the cingulate cortex.



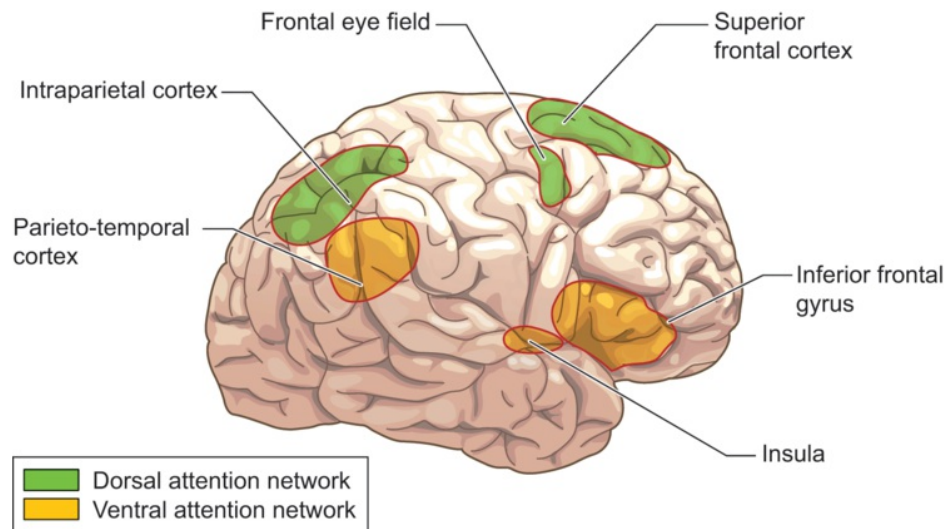


Figure 10.11 Network models of attentional control.

(A) According to the model by Mesulam ([1981](#)), a reticular component provides the underlying level of arousal and vigilance; the posterior parietal lobe provides a sensory map of the world so as to help direct attention to particular locations or objects; the cingulate gyrus regulates the spatial distribution of attention with regard to motivational value; and a frontal component coordinates the motor programs for exploration, scanning, reaching, and fixating.

(B) According to the model by Posner and colleagues (Posner and Rothbart, [2007](#)), there are three main attentional networks in the brain. The one for alerting, which is shown in green, is involved in achieving and maintaining a high state of sensitivity to incoming stimuli. Another, primarily associated with orienting and shown in purple is involved in aligning attention to the source of a sensory signal. The third, shown in red is involved in executive aspects of attention, which directs how attention is directed according to an individual's goals or desires. These systems are hypothesized to be modulated by the neurotransmitters norepinephrine, acetylcholine, and dopamine, respectively (from Postner and Rothbart, [2007](#)).

(C) According to Corbetta and Shulman ([2002](#)), visual attention is controlled by two networks. One network, the dorsal attention network including the superior frontal cortex, frontal eye fields, and intraparietal cortex, is involved in goal-directed aspects of attentional control. The other is a ventral system, mainly lateralized to the

right hemisphere, that is composed of inferior frontal and temporoparietal regions. It is specialized for the detection of behaviorally relevant stimuli.

Because this model views attention as being supported by an interconnected neural network, it has three important implications for understanding how brain damage may affect attention. First, it implies that a lesion confined to a single brain region may affect not only attentional behaviors, but other behaviors as well. For example, although frontal regions are part of the attentional network, they are also involved in executive functions. Second, the same complex function can be impaired as a result of lesions in different locations. For example, as we discuss in more detail shortly, hemineglect has been reported after lesions to many different regions of the brain. Third, the most severe disruption of a complex function will be observed after damage to more than one region that is included in the network. Thus, neglect would be more severe if damage occurred to both frontal and parietal regions rather than just parietal regions.

Altering, Orienting, and Executive Attention

Another prominent model argues that attention can be divided into three somewhat separable systems that are involved, respectively, in alerting, orienting, and executive attention (see [Figure 10.11B](#); Posner and Rothbart, [2007](#)). According to this model, one subsystem is responsible for alerting, which involves achieving and maintaining a state of high sensitivity to incoming information. This subsystem allows the brain to maintain a tonic alert state and to respond phasically to signals that warn of upcoming events. The alerting system relies on the locus coeruleus, thalamic regions, and a right-hemisphere system involved in overall arousal, and is linked to the neurotransmitter norepinephrine. A second subsystem, the orienting subsystem, involves aligning attention with the source of sensory signals, and selecting among multiple sensory inputs. The second subsystem, according to this model, relies on the superior colliculus, parietal areas, and the frontal eye fields, and is linked to the neurotransmitter acetylcholine. The third subsystem, one that supports executive attention, controls how

attention is directed according to an individual's goals or desires, including detecting and resolving conflict. This system is composed of the basal ganglia, lateral ventral prefrontal regions, and the anterior cingulate, and is thought to rely on dopamine.

Some evidence from lesion patients supports such a distinction. Specific deficits in alerting were found in patients with damage to the brainstem (home of the reticular activating system) and the thalamus, while patients with lesion to the right pulvinar and right temporoparietal cortex had difficulty with orienting. Finally, damage to prefrontal and premotor regions was associated with difficulty with executive function. Yet lesion location could not predict the pattern of specific deficits in about half of the patients, suggesting that these systems may not be entirely dissociable (Rinne et al., [2013](#)).

In fact, other evidence suggests that aspects of processing in one system may affect the other systems. For example, when a cue directs attention to an incorrect location of a subsequent target, a process supported by the orienting system, it is harder for participants to resolve interference from conflicting information, a process supported (according to this model) by the executive system (Fan et al., [2009](#)). If the two systems were totally separate, these effects should not be linked. Moreover, while activation of the locus coeruleus was specifically associated with alerting, and activation of the superior colliculus and frontal eye fields was specifically associated with orienting, activity in regions of the frontoparietal network were observed across all three types of operations: those involved in alerting, orienting, and executive control (Xuan et al., [2016](#)). Thus, we see that even models that attempt to segregate attentional functions to different brain regions ultimately must account for their interdependence.

Selection of Goals Versus Detection of Behaviorally Relevant Stimuli

Another model posits two partially segregated networks that carry out different attentional functions: the dorsal attention system and the ventral attention system (Corbetta and Shulman, [2002](#)). The dorsal attentional system is composed of portions of the intraparietal cortex, superior frontal cortex, and frontal eye fields. This system prepares and applies goal-directed (top-down) selection for stimuli and responses. The

ventral subsystem includes the temporoparietal cortex, the inferior frontal cortex, and the anterior insula, mainly lateralized to the right hemisphere. This subsystem is specialized for the detection of behaviorally relevant stimuli, particularly when the stimuli are salient or unexpected. In this model, the dorsal system is more involved in top-down attentional control and the ventral system is more involved in bottom-up aspects of attention.

Why have two such systems? If we could direct our attention only to goals, places, or objects that we had selected in a top-down manner, we would likely miss salient environmental effects that we hadn't anticipated. In other words, the ventral frontoparietal network works as a "circuit breaker" for the dorsal system, "resetting" attention when important new events occur. The locus coeruleus may drive the ventral attentional system, implicating noradrenaline in the reset process. For example, when people were shown faces subliminally so that they could not consciously detect them, increased activity was observed in the superior colliculus, pulvinar, locus coeruleus, and amygdala when the faces had a fearful expression rather than a neutral one. The authors proposed that the colliculo-pulvinar pathway to the amygdala allows a subliminal fear signal to be processed, which in turn activates the locus coeruleus to act as a circuit breaker (Liddell et al., [2005](#)). This study illustrates how the ventral system could play an important role in redirecting attention so that we do not end up with tunnel vision based on current goals and objectives.

But the interaction can go in the opposite direction as well. A good illustration of this fact comes from a study in which TMS was applied during the recording of brain activity via functional neuroimaging. When TMS was applied to the intraparietal sulcus, a region of the dorsal attentional system, reduced activity was observed in the temporoparietal junction, a portion of the ventral attentional system (Leitão et al., [2015](#)). The interaction of these two systems allows for the human brain to be flexible in the degree to which bottom-up or top-down biases may influence attentional control at any one point in time (Vossel et al., [2014](#)).

In sum, while all of these models provide useful heuristics to consider how

attentional control may be implemented in the brain, they should not be taken as indicating strong functional divides. As is becoming clearer with more research, attention acts by modulating brain function across different brain regions in different ways at different times to meet task demands.

The Default Network: The Lack of Attention or Internal Attention?

What occurs when we have lapses of attention? Is it just that the structures we discussed are off-line or taking a nap? For many years, that is what researchers assumed. However, one viewpoint has argued that there is a brain system that works in opposition to the brain regions engaged by attentional demand (Raichle, [2001](#), [2015](#)). This system has been referred to as the “default network,” presumably because it is activated when the brain is in “default mode” rather than being attentionally engaged. It is sometimes also referred to as the “task negative network” as compared to those regions engaged during task performance, which are referred to as the “task positive network.”

According to this model, the default network consists of the regions shown in [Figure 10.12](#), including medial orbitofrontal regions, superior frontal regions, posterior cingulate cortex, specific portions of the inferior parietal lobe, and portions of the medial temporal lobe, including the hippocampus. Activity in this network decreases at the same time that activity increases in many of the regions we have discussed in this chapter, including the dorsolateral prefrontal cortex, SMA, other portions of the inferior parietal region, frontal eye fields, and the intraparietal sulcus (Fox et al., [2005](#)). In other words, activity in the default network seems to have a reciprocal relationship with activity in attentional control structures (see [Figure 10.13](#)).

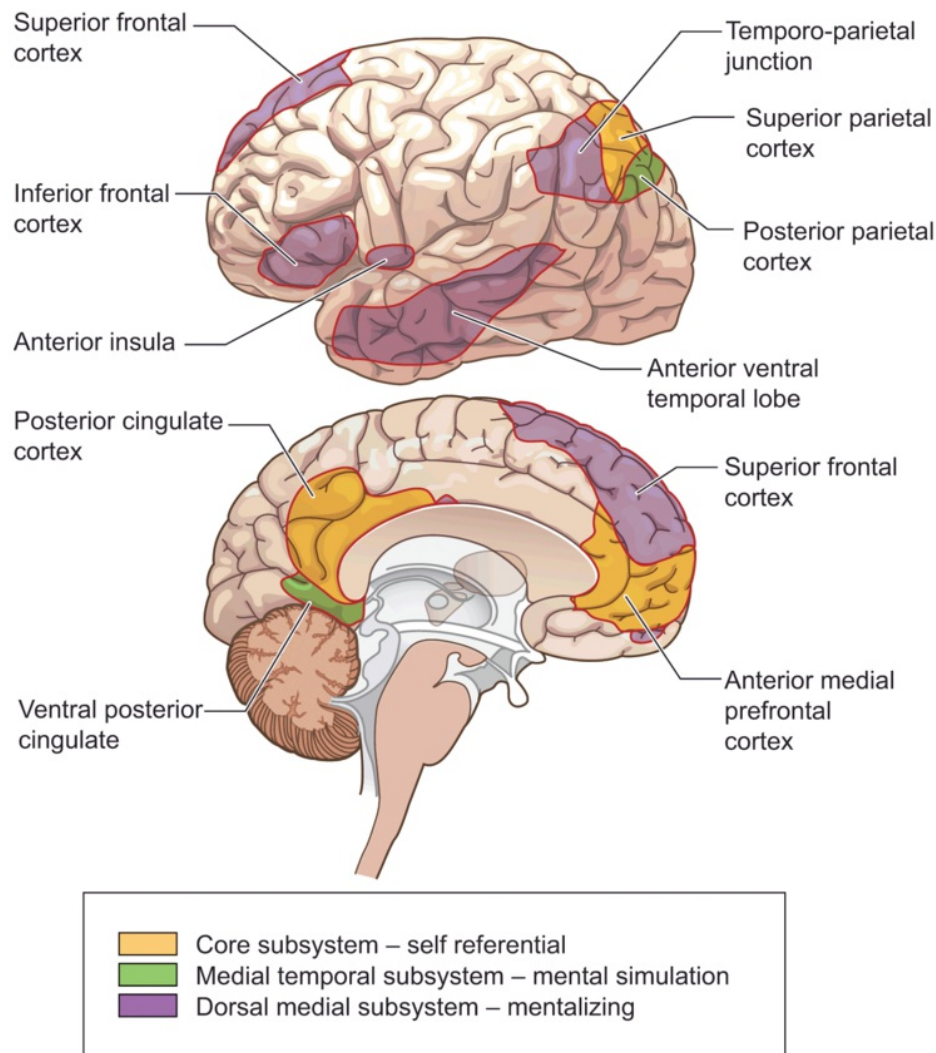


Figure 10.12 The main regions involved in the so-called “default network” and its division into three subsystems.

It has been proposed that this network is involved when attention and processing are directed internally, rather than to the external world. It has been proposed to have three subsystems: a core region (shown in orange) that allows for the processing of self-referential information; a medial temporal subsystem (shown in green) that is involved in constructive mental simulation; and a dorsal medial subsystem, that is involved in the process of inferring or reflecting upon the mental states of others (shown in purple).

(from Andrews-Hanna et al., [2014](#))

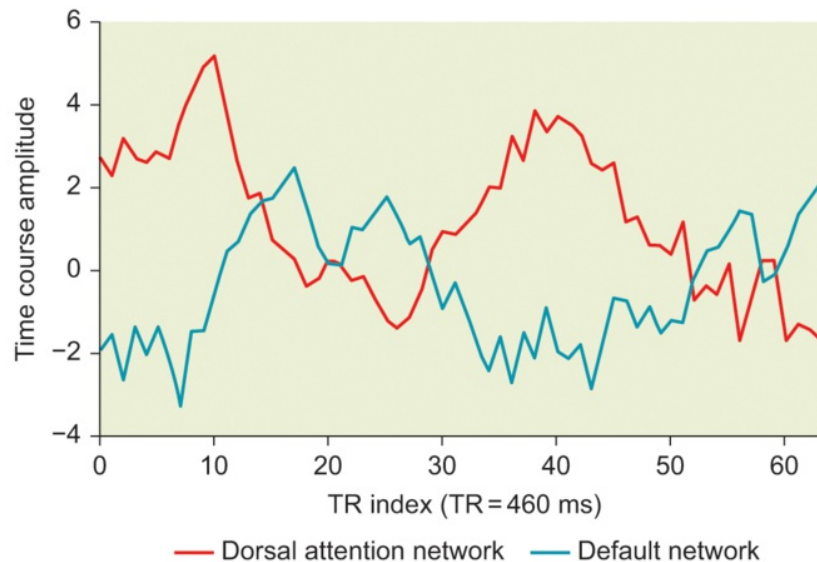


Figure 10.13 The reciprocal relationship in activity between the default network and the executive control network.

Shown here is the relationship between activity in the default network (shown in green) and the dorsal attention network (shown in red) over time for a representative person. Notice that as activity increases in the default network, it decreases in the dorsal attention network, and vice versa.

Further evidence for the idea that the default network is associated with the lack of attention comes from the study of attentional lapses. When people have lapses in attention (as indicated by longer reaction times and higher error rates on specific trials), there is more activation of the default network than when they appear to be attentive (Weissman et al., [2006](#)). Thus, the ability to pay attention seems to rely not only on engagement of attentional systems, but also on disengagement of the default mode network.

Other perspectives on the default network argue that it is engaged not so much when our mind is “blank” or we are at rest, but rather when we direct our attention inward, such as when we turn to concentrate on our internal thoughts or ideas, rather than focusing on the outside world (Andrews-Hanna et al., [2014](#)). Consistent with this viewpoint, activation is observed in the default network when people must retrieve particular episodes from their past, think about or plan future events, imagine novel

scenes or situations, infer the mental state of others, make appraisals about themselves (e.g., “Was I being totally honest?”), and reason about moral dilemmas and other scenarios.

Analyses of the clustering of activity in regions within the default network during tasks and at rest suggest that it can be divided into three subsystems. The first, considered the core regions and consisting of anterior medial prefrontal cortex and the posterior cingulate cortex, has been proposed to be involved in allowing personal meaning to be constructed from salient information. These areas become active when a person needs to think about information in reference to themselves: who they are and what they value. A second subsystem, the medial temporal subsystem, involves portions of the medial temporal lobe, the ventral posterior cingulate cortex, and posterior parietal region. This system is thought to be involved in constructive mental simulation, allowing people to use memories from their past to help simulate and imagine novel situations and/or the future (refer back to Chapter 9, page [284](#)). The third subsystem, the dorsal medial subsystem, involves portions of the superior and inferior frontal cortex, anterior insula, temporoparietal junction, and anterior ventral temporal regions. It is thought to play a role in conceptual processing, and mentalizing, which is the metacognitive process of inferring or reflecting upon the mental states of other people and/or one’s self (refer back to [Figure 10.12](#)).

As you might imagine from this description of the functions of the default network, researchers are now trying to better understand how activity in this network might influence a variety of mental processes, ranging from mind-wandering to creativity (Smallwood and Andrews-Hanna, [2013](#)). Moreover, they are trying to learn more about this network because the ability to adaptively control internal thought may be disrupted in certain populations, such as those who have mental illness. Understanding the functions of the default network, therefore, is likely to be an important topic of research in the coming years.

Hemineglect: Clinical Aspects

We spend the rest of this chapter investigating hemineglect, the syndrome described in its opening vignette. Hemineglect is one of the syndromes in which attentional dysfunction most prominently and commonly occurs. First we describe the clinical aspects of neglect and then we discuss how this syndrome has increased our understanding of the cognitive neuroscience of attention (for good short reviews, see Adair and Barrett, [2008](#); Milner and McIntosh, [2005](#)).

Clinical Features

In this section we discuss the clinical features of neglect, first by describing the typical way in which this disorder is manifested. We then examine the features in a bit more detail to illustrate that the disorder cannot be explained merely as a consequence of sensory deficits, but rather reflects a disruption in attention.

Typical Manifestation

As mentioned previously, hemineglect is a syndrome in which individuals ignore, or do not pay attention to, the side of space contralateral to their lesion. The side of space ignored is usually defined with reference to body midline, but neglect may occur with regard to other spatial reference frames as well (e.g., information to the left of the head's midline when the head is not at body midline). This inattention is manifested regardless of the modality in which information is presented. Depending on the severity of hemineglect, patients might fail to notice items on the left side of the world (i.e., spatial neglect), draw the left side of objects (i.e., allocentric neglect), or use the left side of the body (i.e., personal neglect). In severe cases, patients may even deny that the left side of the body belongs to them (for review see Vallar and Bolognini, [2014](#)).

[Figure 10.14](#) shows one simple task often used to detect hemineglect, which is the line bisection task in which individuals are asked to place a mark in the middle of the line. Patients with hemineglect usually bisect the line far to the right as if the left half of

the line did not exist! Similarly, in an item cancellation task individuals are asked to cross out all the items (such as Xs) on a sheet of paper in front of them. Typically, they only do so for items on the right side of the page.



Figure 10.14 Typical example of line bisection by an individual with hemineglect.

Because the person with hemineglect ignores the left half of space, the line is bisected far to the right, as if the line extended only from its midpoint to its right endpoint.

Symptoms of neglect may vary depending on the time since the brain damage. The degree of neglect is usually severe at first: all items on the neglected side of space are ignored. Within weeks to months, this profound neglect usually dissipates, such that a single item on the neglected side of space can be detected. Nonetheless, if there is competing information, such as when identical stimuli are presented at the same time in both visual fields (a condition known as double simultaneous stimulation), the individual tends to neglect the stimulus on the left. This phenomenon is often called hemi-extinction because the information on the neglected side of space is extinguished from consciousness. This phenomenon reinforces the idea that competition plays an important role in how attention is directed.

While neglect can occur after left-hemisphere lesions, it is much more commonly observed after right-hemisphere stroke (Becker and Karnath, [2007](#)) and is often more severe (Ten Brink et al., [2017](#)). In other words, neglect is typically observed for the left rather than right side of space. Classically, neglect was considered to be observed after vascular damage to the supramarginal gyrus of the parietal region, which extends into subcortical regions (e.g., Vallar and Perani, [1986](#)). Consistent with such thinking, TMS over the right inferior parietal region induces hemi-extinction in neurologically normal individuals (Dambeck et al., [2006](#)), as does TMS over the temporoparietal junction, an effect not observed with TMS over the right temporal gyrus (Meister et al., [2006](#)).

More recently, however, there is an emerging consensus that neglect appears to be a heterogeneous disorder. Different measures of neglect, ranging from line bisection to item cancellation, are associated with damage to diverse regions of the right hemisphere (Molenberghs et al., [2012a](#)) (see [Figure 10.15](#)). As such, neglect is unlikely to arise from damage to just one region in the brain but rather results from damage to a network of interconnected regions in the right hemisphere (Bartolomeo, [2007](#); Corbetta and Shulman, [2011](#); Karnath and Rorden, [2012](#)), which includes the posterior inferior parietal regions, superior temporal regions, and ventrolateral prefrontal regions (see [Figure 10.16](#)). Importantly, disrupted connectivity, as can be caused by damage to underlying white matter, appears to be critical to producing the syndrome. Damage to the superior longitudinal fasciculus, which connects the posterior and anterior portions of this network, is associated with long-lasting neglect (Lunven et al., [2015](#)).

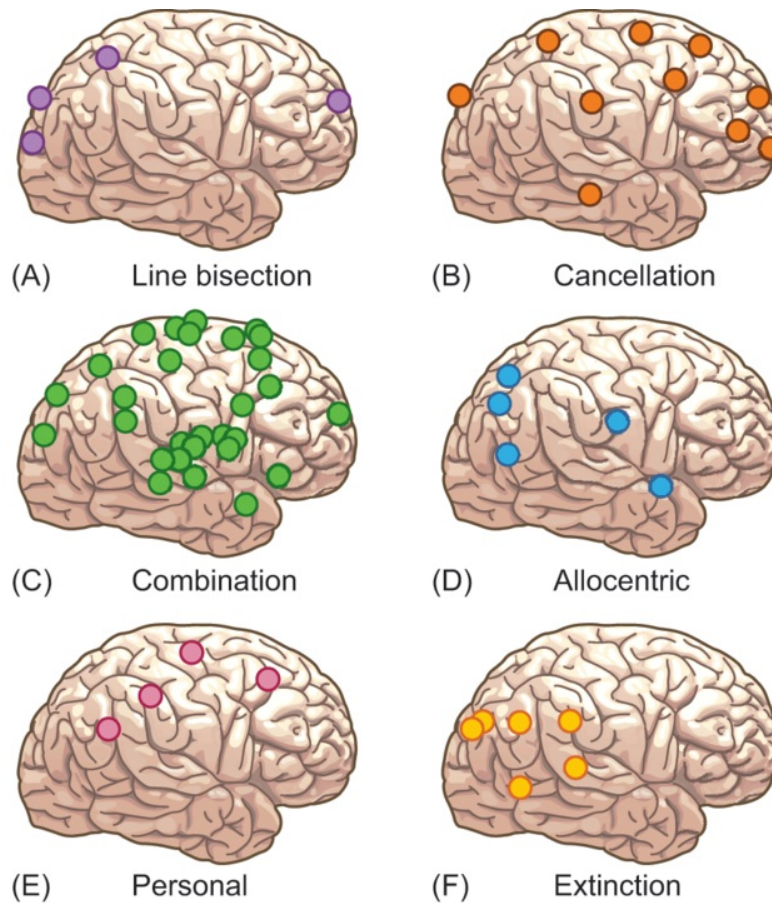


Figure 10.15 Location of lesions that are associated with behavioral manifestations of neglect as assessed through different tests.

(A) Altered line bisection. (B) Altered letter cancellation. (C) A combination of assessments. (D) Allocentric (i.e., object-based) neglect. (E) Neglect of part of one's person and (F) extinction under conditions of dual stimulation.

(from Molenberghs et al., [2012a](#))

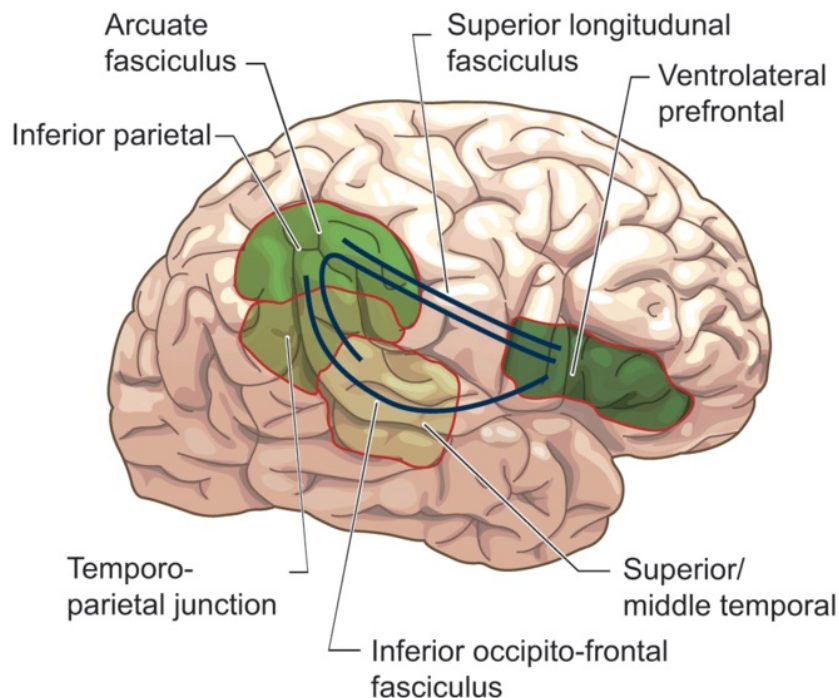


Figure 10.16 The system of brain regions wherein damage is associated with neglect.

In general, most individuals with hemineglect have sustained damage to some portion of a right-sided network including the inferior parietal lobe, the temporoparietal junction, posterior portions of the superior and middle temporal cortex and lateral prefrontal and premotor cortices. Generally, there is damage to the underlying white matter connecting posterior and anterior portions of this circuit, which typically involve the superior longitudinal fasciculus (dorsally) and/or the arcuate fasciculus and inferior occipitofrontal fasciculus (ventrally).

Not Due to Sensory Deficits

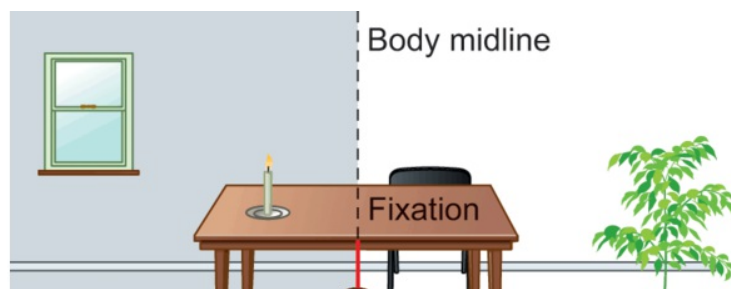
So far we have presented the neglect syndrome as a deficit in attentional processing, but we have not directly discussed the evidence to support this assertion. In this section, we discuss findings demonstrating that neglect cannot be attributed to deficits in sensory processing. In the [next section](#), we discuss evidence showing that neglect is modulated by attentional factors.

To evaluate the possibility that neglect could result solely from deficits in sensory processing, let us reconsider the opening vignette of this chapter. Initially you may have

thought that the gentleman's odd behavior might be explained by right-hemisphere damage that interfered with receipt of sensory information from the left side of space and motor control on the left side of his body. On closer investigation, though, you can see that this explanation is not plausible. He could perform motor acts competently, as evidenced by his ability to shave, shower, dress, and eat. Despite such competence, however, motor acts were confined mainly to the right side of his body. Thus, the motor acts themselves were probably not disrupted. Rather, the ability to direct these acts to the left side of the body was impaired.

Is it possible that a sensory deficit in the visual modality could explain his behavior? You might hypothesize that he had a dense hemianopia of the left visual field (LVF) that left him functionally blind for all information to the left of fixation. Yet this explanation cannot account for a general inattention to visual information to the left of body midline, because patients with hemianopia can process visual information on the left side of space. They do so simply by moving the center of their gaze to the far left.

For a fuller appreciation of this point, look at [Figure 10.17A](#). Assume that you have left hemianopia, are sitting at the center of the table, and want to make sure that the candle you lit on the left side of the table is not dripping wax. If your gaze is fixed straight ahead, you will be blind to all information to the left of body midline, including the candle. However, simply turning your head and fixating your gaze on the left edge of the table, as shown in [Figure 10.17B](#), will enable you to see the candle because it now falls entirely within your right visual field (RVF). Thus, even though the candle remains to the left of body midline, it can be perceived merely by changing the point of visual fixation. Therefore, visual deficits cannot account for the fact that patients with hemineglect ignore what is on the left side of space.



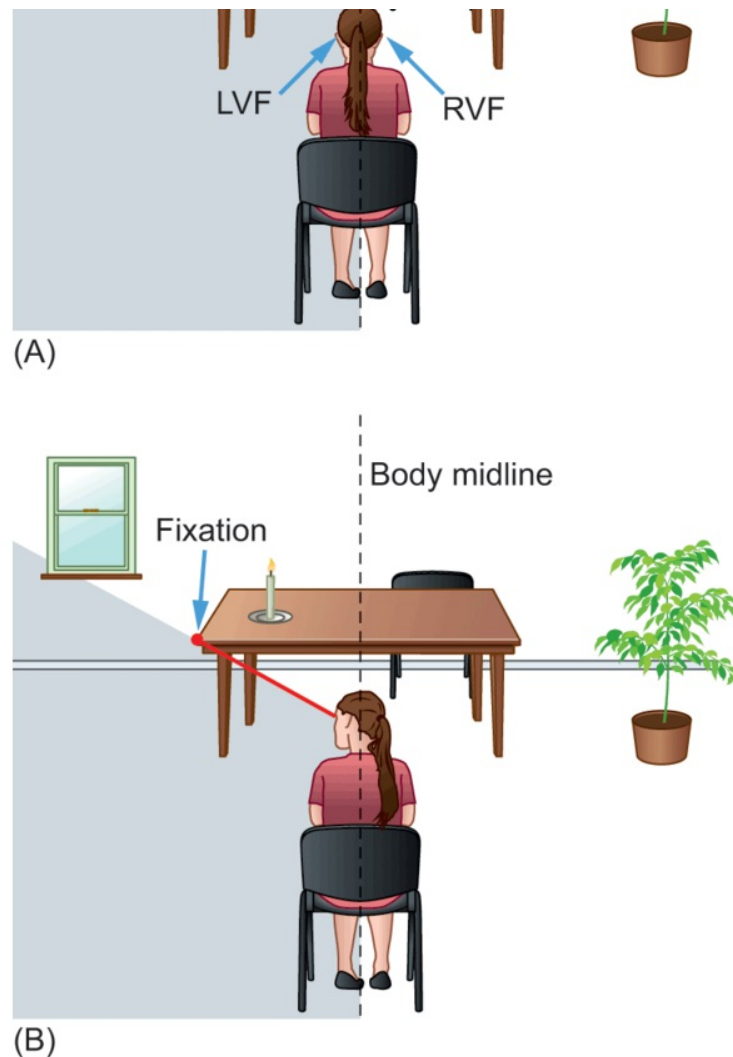


Figure 10.17 The influence of head position on the information that falls in each visual field.

(A) When someone is looking straight ahead, information to the left of body midline falls in the left visual field (LVF) and information to the right of body midline falls in the right visual field (RVF). If the individual has hemianopsia for the LVF (gray region), the candle in this picture will not be visible. (B) However, the individual can view the candle by simply turning her head so that the candle now falls within the good visual field, the RVF. Although patients with hemineglect who simultaneously have visual field defects could use such a strategy, they do not, because they ignore the left side of space.

Our analysis so far should make you skeptical of the idea that hemineglect can be explained by sensory loss in the visual modality. Is it possible, however, that patients

with hemineglect are relatively insensitive to all sensory material received by the damaged hemisphere? We now entertain this hypothesis just long enough to disprove it!

If this hypothesis were true, then the severity of neglect would be predicted by the degree to which information in a given modality is processed by the contralateral hemisphere. For the purposes of this discussion, let us assume that the person is ignoring information on the left as the result of a right-hemisphere lesion. Because only the right hemisphere receives visual and somatosensory information from the left, this hypothesis would predict neglect of visual and somatosensory information from the left, but intact processing of this same type of material from the right. In the auditory modality, inattention to material on the left would be less severe because some information from the left ear projects ipsilaterally to the intact left hemisphere. In addition, some neglect of auditory information on the right would be expected because the right hemisphere would be unable to proficiently process information from the right ear that is received through ipsilateral pathways. Finally, because the left nostril projects to the left hemisphere and the right nostril to the right hemisphere, no neglect would be observed for smells on the left, but neglect would be evident for smells on the right.

In other words, if the neglect resulted from an inability of the right hemisphere to process sensory information, it would be exhibited by an extreme insensitivity to visual information in the LVF and tactile information from the left side of the body, less extreme neglect for auditory information on the left side of space, and no neglect for olfactory information on the left side of space. But such variations in the degree of neglect across modalities are not observed in cases of hemineglect. Instead, information from the contralateral side of space is generally ignored regardless of whether it is presented in the visual, tactile, auditory, or olfactory modality (Jacobs et al., [2012](#)). Moreover, the severity of neglect in one modality, such as the visual modality, correlates with the severity of neglect in another modality, such as the auditory modality (Pavani et al., [2003](#); Pavani et al., [2004](#)). These pieces of evidence demonstrate that neglect does not appear to have a sensory basis.

Modulated by Attentional Factors

Because we know that hemineglect is not the result of sensory malfunction or damage, we now examine the evidence demonstrating that it arises specifically from a disruption in attentional processing. Let's return to the scenario at the beginning of this chapter. One odd aspect of the gentleman's behavior was that information on the left side of space that was ignored on one occasion was not ignored on others. So, although he initially ignored his hash browns and bacon, he eventually ate them, but only after his attention had been drawn leftward by the sound of the crashing dishes.

As this scenario suggests, neglect can be moderated by attentional factors. According to anecdotal reports, particularly salient or emotional information in the neglected half of space (such as a long needle in the hands of a nurse) will not be ignored. Even in experimental situations, neglect can be diminished by the manipulation of attention. For example, a classic sign of hemineglect is the inability to bisect a line correctly (refer back to [Figure 10.14](#)). Patients with hemineglect most often place the "halfway" point about one-quarter of the way from the line's right end and three-quarters of the way from the left end (e.g., Reuter-Lorenz and Posner, [1990](#)). They act as if the line extends only from the middle to the right and has no left side. However, line bisection can be improved (although it is still not totally accurate) if attention is first drawn to the left side of space by placing a salient marker that must be identified before the line is bisected, such as a digit or letter that must be named, at the left edge of the line (e.g., Riddoch and Humphreys, [1983](#)). Similarly, if the end of the line has a simple schematic face with eyes gazing left, patients show reduced neglect compared to eyes gazing straight ahead or to the right (Bonato et al., [2008](#)) (see [Figure 10.18](#)).



Figure 10.18 Attentional cues to the left side of space can reduce neglect.

Patients with neglect do not bisect the line as far to the right when a cue of face has a leftward gaze compared to when the eyes are facing right, with central gaze being intermediate.

Furthermore, if information on the neglected side of space is critical for the understanding or comprehension of material, it tends to receive attention. For example, if a patient with hemineglect for the left side of space sees the word antiballistic centered on the page, he or she is much more likely to read the word as ballistic, even though the letters to the right of midline are only llastic. Thus, patients with hemineglect attend to information from the left side of space to the degree that it is needed to devise a reasonable interpretation of the available sensory information.

Finally, motivational factors can also mitigate the degree to which attention is allocated to the left. In one classic case study, a patient with hemineglect was asked to perform a letter cancellation task that required crossing out all the As on a page full of letters. On the first occasion, he was simply told to perform the task; on the second occasion, he was promised a certain amount of money for every A correctly detected. When he was provided with a motivation to direct attention to the left side of space, his neglect was reduced, as indicated by his ability to detect more As on the second occasion than on the first (Mesulam, [1985](#)). Subsequent work in a larger group of patients with right-hemisphere lesions indicates that indeed motivational factors, such as monetary reward, can reduce neglect on standard clinical measures such as an item cancellation task (Malhotra et al., [2013](#)).

Thus, we know that neglect can be decreased by manipulations drawing attention to the left. These manipulations include external factors, such as the presence of particularly salient items or emotionally charged information. Attention to the left can also be increased by internal factors, such as a pressing motivation to process the left side of space or the need to do so to make sense of the world.

Theories Regarding the Underlying Deficit

One of the most striking aspects of hemineglect is that affected patients seem to have little awareness that they are ignoring one side of space. To better appreciate this phenomenon, consider, as an analogy, how you usually conceptualize the area of space behind your head. Because your attention is focused on the world in front of you, generally you give little thought to the region behind you. Even if instructed to pay attention to what is behind you, you might start out by looking over your shoulder every few seconds, but would soon stop doing so. However, you'd probably do it for a longer period if you were paid a certain amount of money every time you reported on an event that occurred behind you. You might also pay attention to the world behind you if some extremely significant information were coming from that region, such as the sound of quickly approaching footsteps when you were walking down a dark street alone at night. The patient with hemineglect treats one side of space the way you normally treat the space behind your back.

Researchers have tried to discover why this profound neglect occurs. One suggestion is that these patients lack an internal mental representation of the neglected side of space. According to this view, that side of space doesn't even exist for these patients! This idea is nicely illustrated by a particularly ingenious study conducted by Bisiach and Luzzatti (1978), involving two patients from Milan, Italy, who had hemineglect for the left side of space. While the patients were in their hospital rooms, the researchers asked them to imagine in their mind's eye an extremely famous plaza, known to almost all inhabitants of Milan, that contains a variety of buildings, including

the city's renowned and ornate cathedral. First, the patients were asked to imagine standing at the end of the plaza opposite its imposing cathedral and to describe what they saw. The landmarks that the patients mentioned are designated by red circles on the map of the square shown in [Figure 10.19A](#).

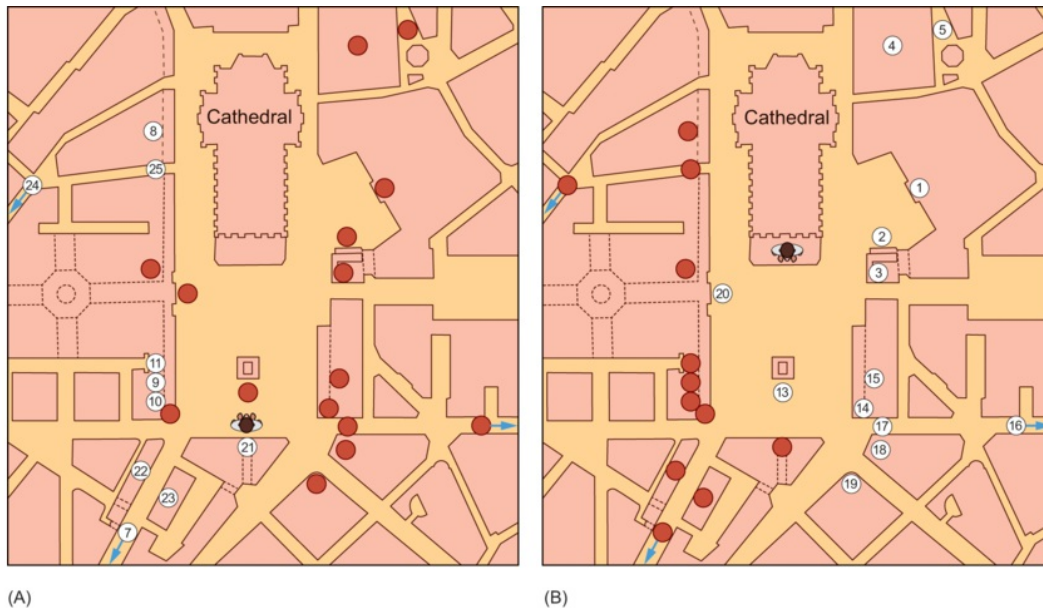


Figure 10.19 Maps indicating which structures were reported by patients with hemineglect when they imagined standing in the Piazza del Duomo in Milan, Italy.

The position in the plaza where the individual imagined himself or herself to be standing is marked with a black circle. The landmarks that the patients described are designated by filled circles. (A) The landmarks mentioned by patients when they imagined themselves facing the cathedral. These landmarks are situated mainly on the right. (B) The landmarks mentioned when the patients imagined themselves standing on the steps of the cathedral and facing away from it. Once again, mainly the landmarks on the right are mentioned. These individuals' memories for the square are intact because they mention most of the square's major landmarks across the two imagined positions.

Notice that the patients could aptly describe the major landmarks on the right but not those on the left. Why not? Perhaps in their minds' eye, they were exhibiting neglect of

information on the left. But there was an alternative explanation – their memory for the buildings situated in that part of the plaza was poor. To distinguish between these two possibilities, the researchers next asked the patients to imagine being at the opposite end of the plaza – standing on the steps of the cathedral with their backs toward it – and then to describe the plaza. As shown in [Figure 10.19B](#), they described a whole new set of landmarks: those that were previously to the left but were now to the right.

We can draw a number of conclusions from this study. First, clearly the patients' memory for the entire plaza was fine, as all aspects of it were described across their first and subsequent imaginings of the plaza. Second, the patients were missing the conception of one side of space, in this case the left, because from either mental vantage point they failed to report information on the left. Third, the attentional disruptions observed in hemineglect need not be driven by external stimuli. In this case, the patients were in their hospital rooms, not the plaza, imagining the square. These findings imply that patients with hemineglect fail to represent one side of space or fail to pay attention to one side of their mental representations of the world.

We can then ask whether there is a complete and total failure to represent the left side of space, or whether that representation is distorted in some systematic manner. One theory, known as the anisometry hypothesis, argues that the representation of space is distorted such that the representation of space toward the periphery is more and more compacted (Bisiach et al., [2002](#)). Other theories of hemineglect consider it to arise from competition between the hemispheres (e.g., Kinsbourne, [1970](#)). This viewpoint suggests that the problem is not so much that the left side of space is distorted for these individuals, but rather that the pull of sensory stimuli on the nonneglected side of space is so salient as to prevent these patients from attending to the information on the neglected side. The greater the imbalance, the more attention is drawn to the ipsilesional side of space. In addition, there is a gradient of attentional neglect, such that the further into the contralateral field an item is located, the greater the neglect (Kinsbourne, [1987](#)).

Consistent with this idea are a number of pieces of evidence. First, patients with parietal lesions often have difficulty disengaging attention from the nonneglected field. This phenomenon can be illustrated by the cueing paradigm in [Figure 10.20](#). In this task, a cue identifies with a high degree of probability where the subsequent target will appear. When presented with a cue in the neglected field, patients with neglect do not have much difficulty detecting the subsequent target. In this condition, there is no competing information in the nonneglected field from which attention must be disengaged. However, if the cue is presented to the nonneglected field followed by a target in the neglected field, there is a large increase in reaction time, above and beyond that typically observed for neurologically normal individuals. These patients appear to have particular difficulty in disengaging their attention from the competing information in the nonneglected field (Posner et al., [1984](#)). Likewise, we discussed how the long-lasting deficits in hemineglect are likely to occur under conditions of double simultaneous stimulation, once again a condition in which there is competing information in the nonneglected field.

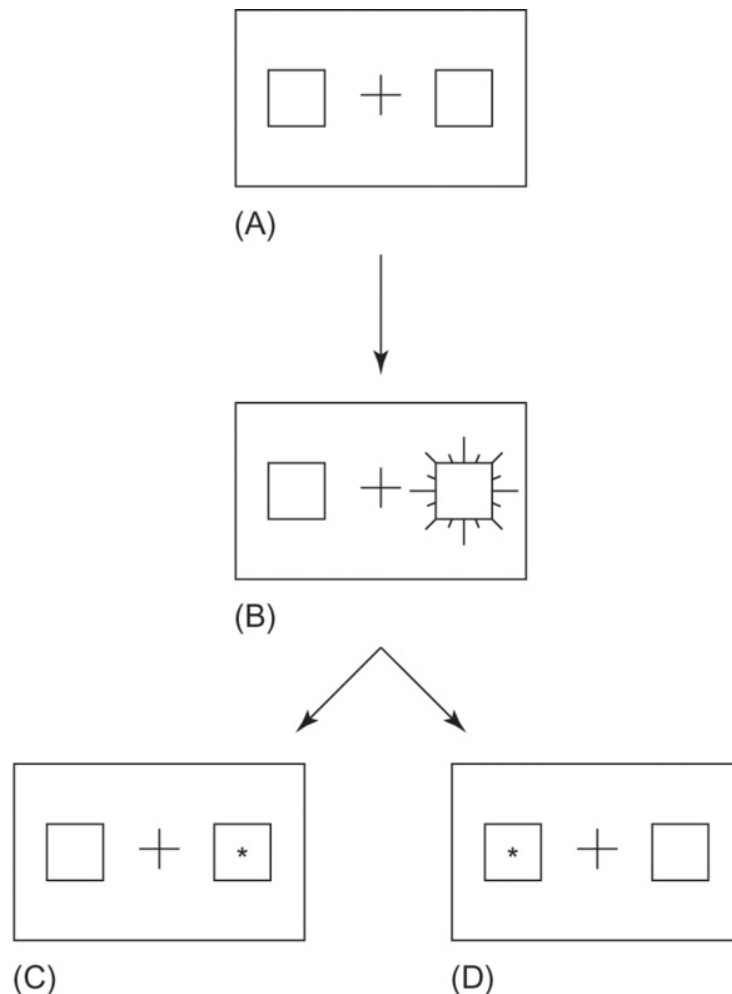


Figure 10.20 A classic paradigm for measuring spatial attention that reveals deficits in individuals with hemineglect.

(A) The individual is told to fixate on a central location (the cross) for the duration of the trial. (B) At some point, a cue occurs, in this case the brightening of a peripheral box. This cue predicts with a high degree of accuracy the location of the subsequent target. The target to which the individual must respond (an asterisk) appears after a variable time interval. Two types of trials are given: those in which the cue correctly predicts the location of the subsequent target, valid trials (C); and those in which the cue incorrectly predicts the location of the subsequent target, invalid trials (D). Responses to invalid trials take longer because the individual must move attention from the cued location to the actual location of the target. Individuals with hemineglect have specific difficulty on invalid trials when the cue is presented in the non-neglected field.

An interesting demonstration of the degree to which information in the nonneglected field influences performance was provided by a study in which patients with unilateral neglect performed two versions of a cancellation task often used to assess hemineglect (Mark et al., [1988](#)). In this task, a series of lines are randomly distributed across the page, and the person must “cancel” as many Xs as possible. In one version, individuals canceled the targets on a dry-erase board by writing over them in darker-color ink. In this way, the lines remained even after they were canceled. In the second version, individuals were given an eraser and canceled the lines by erasing them. The neglect for left-side stimuli was less severe in the second condition than in the first. Because cancellation of the lines by erasure decreased the number of items in right hemi-space, there were fewer items from which attention needed to be disengaged, and hence the neglect was less severe.

These data can also be interpreted to suggest that hemineglect results from an uneven competition between the hemispheres for controlling the direction of attention. As we learned earlier in this chapter, the notion of competition is fundamental to many models of attentional control. When both hemispheres are intact, the competition is equal, but after brain damage, the competition becomes lopsided and hemineglect is observed.

Some of the most compelling data for this explanation of hemineglect come from studies of patients with unilateral brain damage who suffer from neglect and were administered TMS. The researchers reasoned that if neglect occurs because of an imbalance between the hemispheres, then giving TMS to disrupt processing of the intact hemisphere should restore such a balance, and reduce neglect. In fact, that was exactly what they found (Oliveri et al., [2001](#)). Since that point additional studies have demonstrated the utility of this approach (see Fasotti and van Kessel, [2013](#), for review). Corroborative evidence that an imbalance between the hemispheres is linked to neglect is provided by studies using TMS with neurologically intact individuals. When TMS is applied over the parietal region to deactivate it, extinction is observed for information in the contralateral space (see Oliveri and Caltagirone, [2006](#)). Conversely, giving TMS

to facilitate brain activity increases attention to the contralateral field (Kim et al., [2005](#)).

Treatment

As we mentioned earlier, although hemineglect may dissipate with time, it rarely (if ever) disappears completely. Hemineglect can be vexing because it interferes significantly with everyday life. For example, think about how having hemineglect would make it dangerous or even impossible to drive a car or cross the street! Finding an effective means of reducing neglect, therefore, is of great clinical interest.

One approach to reduce neglect is to attempt to redress the imbalance in activity across the hemispheres. As we discussed above, this can be done through brain stimulation (using either transcranial magnetic stimulation or transcranial direct current stimulation). Some approaches attempt to down-regulate the activity in the left hemisphere, whereas others try to up-regulate activity in the damaged right hemisphere, and still others try to do both via either TMS or tDCS (Jacquin-Courtois, [2015](#)). While these can ameliorate neglect when a person is connected to a machine seated in the hospital or clinic, there is a need for the effects to continue well past the hospital visit. Initial trials indicated that stimulation-induced reduction in neglect was only transient (Oliveri et al., [2001](#)) or limited to about two weeks of effective time (Brighina et al., [2003](#)). More recent evidence, however, suggests that, at least in some cases, the effects can be longer-lasting (Shindo et al., [2006](#)) and that continued treatment of about a five sessions per week over two weeks leads to noticeable improvement (e.g., Kim et al., [2015](#)).

Other approaches attempt to redress the hemispheric imbalance by using methods that orient attention and action to the left side of space (Kerkhoff and Schenk, [2012](#) for a review). One simple method for reducing neglect is to either actively or passively move the limb on the neglected side of space within the neglected hemi-space (e.g., Frassinetti et al., [2001](#)). A number of other methods work by inducing the illusory subjective feeling that there is a drift or movement rightward, which requires a compensatory

leftward orientation to stabilize the world. Consider, for example, being on a train and watching the world whiz by to your right. You feel the need to orient leftward so as to maintain your visual focus. This is the idea behind optokinetic stimulation (e.g., Vallar et al., [1997](#)) which can have long-lasting effects in both the visual (Kerkhoff et al., [2006](#)) and auditory modalities (Kerkhoff et al., [2012](#)). In this latter technique, hemineglect patients view randomly distributed items, such as lines, dots, or squares, that move in a coherent pattern, and are taught to view these items from right to left with their eyes without moving the head. This therapy increases activity in frontal and parietal brain regions associated with attention, as well as over posterior regions (Thimm et al., [2009](#)). Various studies have found that vibration of the left neck muscles (often referred to as neck-proprioceptive stimulation) also induces the illusion that you are oriented rightward. To correct this feeling, individuals orient leftwards, which reduces neglect (e.g., Johannsen et al., [2003](#)).

Another technique that has been shown to reduce neglect is known as [caloric stimulation](#). It involves introducing water into the ear canal (Rubens, [1985](#)), which then engenders activity in the vestibular canals. Both introducing water that is substantially colder than body temperature to the left ear, or water that is substantially warmer than body temperature to the right ear, results in the eyes orienting toward the left. Obviously, such a method is not practical to use on a day-to-day basis so that more modern techniques utilize galvanic-vestibular stimulation, which involves applying electrical stimulation to the mastoid bone behind the ear because the vestibular nerve runs just below it. This method also reduces the effects of neglect (e.g., Utz et al., [2011](#)). Yet another method is prism adaptation. In this method, patients are trained, while wearing prisms that move the visual world 10 degrees to the right, to point to target items near midline. When the prisms are removed, individuals now point closer to midline than they did before training, as the rightward shift induced by the prisms trained them to orient further leftward (Rossetti et al., [1998](#); Serino et al., [2009](#)).

The methods we have just discussed mainly try to alter attention by bottom-up factors using sensory or motoric stimulation to force attention to be directed to the

neglected side of space. But as we know, attention can be modulated by top-down factors as well. Hence, some therapies for hemineglect try to take such an approach. Top-down approaches try to teach patients to guide their attention with aid from a therapist or through some other method.

One therapy that is top-down in nature is visual scanning training. In this therapy, patients are prompted verbally by a therapist (or family member) to look to the left, leveraging the typically intact verbal abilities of individuals with neglect. Sometimes a metaphor is used to help patients think about how they should be controlling their attention. For example, they may be shown a picture of a lighthouse and told to imagine they are the lighthouse. Their eyes should sweep around their environment, from right to left, much as the light from a lighthouse sweeps across space.

Another approach is to have individuals learn how to successfully navigate the world within the “safe” haven of a virtual reality environment. The virtual reality environment can be used to train patients to compensate for their neglect, training them for example to use their wheelchairs to avoid obstacles, to determine when it is safe to cross a street, or simulating driving conditions (Fasotti and van Kessel, [2013](#)).

While the list of potential methods for ameliorating the effects of neglect are long, as you may have surmised, researchers and clinicians continue to try to improve old approaches or create new ones because at present there is no good tried and true intervention that is simple, practical, and has proven to be long-lasting. Research will continue in the hopes of finding improved treatments to address the core deficits in neglect.

Hemineglect: Implications for Understanding Brain-Behavior Relationships

Now that we have discussed the clinical aspects of hemineglect, we turn our attention to a number of issues regarding brain-behavior relationships that can be illuminated by this syndrome. As already discussed in [Chapter 7](#), evidence from hemineglect patients

allows us to understand that the brain encodes space according to multiple reference frames, since different patients may have neglect to the left of the different midlines (e.g., midline of body or midline of objects). In this section, we explore how hemineglect provides additional evidence for object-based attention, how it expands our understanding of hemispheric asymmetries in attention, and how it provides insights into the degree to which the nervous system processes unattended stimuli. Where relevant, we present converging evidence from other techniques used in cognitive neuroscience.

Attention Based on Objects

Most of our discussion of neglect so far has assumed a spatial framework defined in terms of the body midline. That is, neglect is assumed to occur for information to the left of the body midline. This assumes a conception of space that is centered around the body itself. However, patients can also show neglect for the left half of objects, regardless of where the objects are located in relation to the body. As you remember, earlier in this chapter we discussed how attention can be directed either to certain regions of space or to certain stimuli, such as objects. In this section, we consider how information from neglect patients can inform our understanding of object-based attention.

Indeed, neglect for certain portions of an object provides further evidence for an object-based form of attention. A number of case studies of **object-based neglect** have been reported both for nonverbal material (e.g., Young et al., [1990](#), [1992](#); Behrmann and Moscovitch, [1994](#); Driver et al., [1994](#)) and verbal material (e.g., Caramazza and Hillis, [1990](#); Hillis and Caramazza, [1991](#)). In these cases, the individual neglects the left half of the stimulus (typically an object or word) regardless of the position of the stimulus in space. To appreciate this form of neglect, take a look at [Figure 10.21](#). Individuals with hemineglect are asked to put an X next to all items that are missing a segment and to circle all items without a missing segment. Notice that one patient neglects all items on the left side of the page, but manages to circle all items on the right side of the page that

have a segment missing, even when that segment is on the left. This patient is demonstrating neglect with regard to the spatial position of the item. In contrast, the other patient circles items across the entire page, but does not place an X next to items with a missing segment on the left, showing neglect that is linked to the objects themselves rather than to their spatial position (Ota et al., [2001](#)).

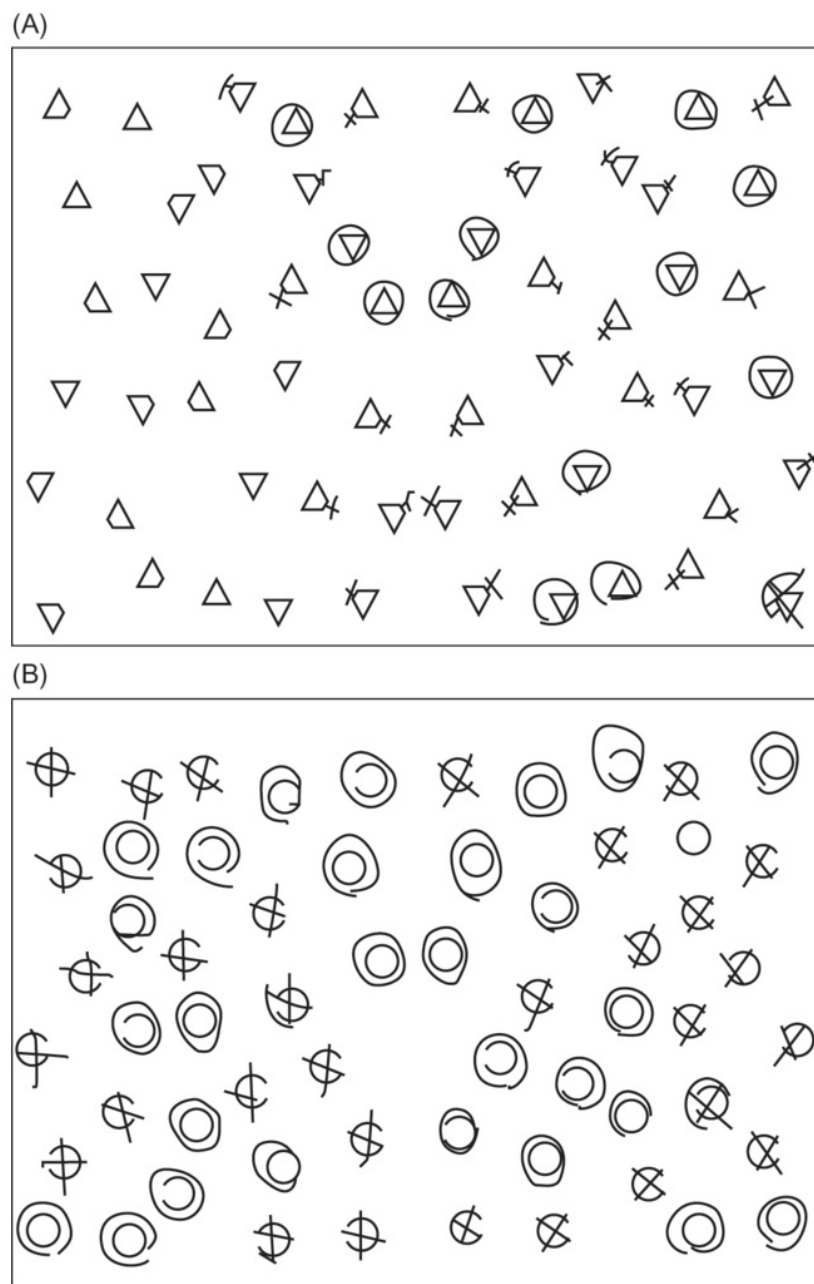


Figure 10.21 Space-based vs. object-based neglect.

In this task, individuals are told to circle all the items on the paper that are complete, and to put an X next to (or through) any item that is missing a part. (A) The behavior

of one patient whose neglect is space-based. Notice that all items on the left side of the page are ignored. For those items on the attended (i.e., right) side of space, incomplete items are marked regardless of whether the missing information is on the left or the right, indicating that there is no object-based neglect. (B) The behavior of another patient whose neglect is object-based. Notice that items are circled across both sides of space, indicating that he does not display space-based neglect. However, this patient fails to put an X next to circles that are missing a portion of their left side, circling them as if they were complete. However, he correctly detects the missing portion of the right side of the circle, putting an X next to those items. As such, he is exhibiting object-based neglect.

(from Ota et al., [2001](#))

In some cases, whether space-based or object-based neglect is observed may depend on the orientation of the object. For example, when words were rotated 180 degrees (i.e., upside down), one patient exhibited neglect with respect to space, but when the words were mirror-reversed, the patient was more likely to show object-based neglect (Savazzi, [2003](#)). In other cases, neglect may vary depending on the reference frame to which the tested individuals are told to attend, such as whether they are told to look across all of space on a computer monitor or to look at particular shapes on the monitor (Baylis et al., [2004](#)). Thus, the type of environment in which information is embedded and how individuals search for the item may affect what type of neglect is exhibited.

Traditionally it has been assumed that these two reference frames dissociate neglect, as earlier studies suggested that a patient could show neglect in an object-based frame of reference but not a space-based one (e.g., Ota et al., [2001](#)). In fact, some authors have argued that damage to different regions of brain tissue underlies neglect for each of these frames of reference (Shirani et al., [2009](#)). In particular, damage that results in object-centered neglect was suggested to involve lesions that are a bit more posterior and inferior to those that typically cause neglect, intruding into temporo-occipital

regions. This location makes sense, as it is closer to object processing regions of the ventral visual processing stream. However, some recent studies suggest that neglect in these reference frames may not be as dissociable as previously thought (Yue et al., [2012](#); Rorden et al., [2012](#)). Regardless of how this debate is resolved, the deficits in hemineglect make clear that attention may be directed in both a space-based and an object-based manner.

Hemispheric Differences in Attentional Control

One of the most striking aspects of the hemineglect syndrome is that it is much more prominent and severe after right-hemisphere damage than after left-hemisphere damage. Theorists have wondered why this is so. Here we discuss some possible explanations.

Some theorists have proposed that the hemineglect exhibited after right-hemisphere damage reflects the effects of two distinct factors: an attentional bias of each hemisphere for information on the opposite side of space and a larger role of the right hemisphere in overall attention and arousal. We now consider each of these two factors and then examine how they might combine to cause the effects observed in hemineglect.

As we discussed earlier in this chapter, each hemisphere exhibits an attentional bias for information located in the contralateral space. To review, when people direct attention to one visual field, such as the left visual field (LVF), the ERP recorded over the occipital lead on the contralateral hemisphere is larger than that over the ipsilateral hemisphere (e.g., Mangun and Hillyard, [1988](#)). When attention has to be shifted among various locations, all of which are restricted to one visual field, activation measured by PET is greatest over left superior parietal and left superior frontal cortex for right visual field (RVF) locations, and over right superior parietal and right superior frontal cortex for left visual field (LVF) locations (Corbetta et al., [1993](#)). Moreover, when task demands activate one hemisphere, this induces an attentional bias to the contralateral side of space, enhancing the processing of material in that location (Kinsbourne, [1974](#)).

Such attentional biases for one side of space can be observed even when items are presented in free vision. Look at [Figure 10.22](#). Which of the two faces looks happier to

you? If you are right-handed, you are likely to have said A. Because the right hemisphere of right-handers is better at the processing of faces and the interpretation of emotional expression, it becomes more activated. This leads to a bias for the contralateral side of space, in this case the left, making the half-face located there more salient and hence judged as happier. Notice that this bias is completely induced by the brain, as the two pictures are mirror-images, which means that on the basis of perceptual factors, there is no reason to perceive one as happier than the other (Levy et al., [1983](#)). On the basis of evidence of this nature, as well as other study findings (e.g., Reuter-Lorenz et al., [1990](#)), each hemisphere appears to have an attentional bias for the contralateral side of space.

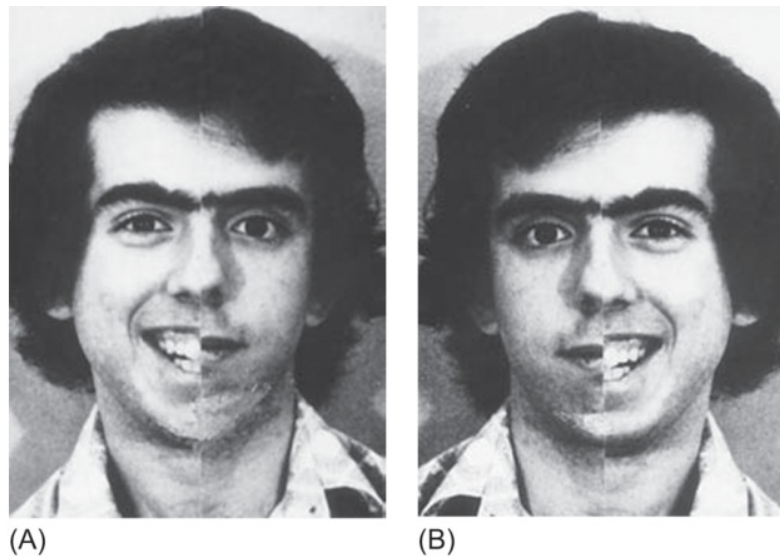


Figure 10.22 Examples of chimeric faces that demonstrate attentional biases to one side of space.

Although these faces are identical except for being mirror-images, most right-handed individuals perceive the face in (A), which has the smile on the left, as happier than the face in (B), which has the smile on the right. Experts think that the left half-face is perceived as more expressive because the right hemisphere is more adept at processing emotional and facial information, which causes an attentional bias toward the left side of space. Hence, information located on the left is perceived as more salient.

Source: "Asymmetry of Perception in Free Viewing of Chimeric Faces," by J. Levy, W. Heller, M. T. Banich, and L. A. Burton, [1983](#), *Brain and Cognition*, 2, p. 406. With permission from Elsevier.

Earlier in this chapter we discussed evidence that the right hemisphere plays a role in overall attention and arousal. Linking this factor more specifically to neglect, patients with hemineglect syndrome often have difficulty with sustained attention, especially in the spatial domain (Malhotra et al., [2009](#)). Moreover, the inability to sustain attention predicts the severity of neglect (Samuelsson et al., [1998](#)).

The manner in which these two factors might combine to produce neglect was demonstrated in a study in which an item-detection task was given to three groups of

people: patients with right-hemisphere damage, patients with left-hemisphere damage, and neurologically intact individuals (Weintraub and Mesulam, [1987](#)). These people were asked to circle as many target items as they could find within a visual display; the results are presented in [Table 10.1](#). As expected, the neurologically intact individuals missed practically no targets on either side of space. The results for patients with brain damage yielded two important findings. First, regardless of whether patients had right- or left-hemisphere damage, they missed more targets on the side of space contralateral, rather than ipsilateral, to the lesion. These results provide additional evidence that each hemisphere is primarily responsible for attention to information in the contralateral hemi-space.

Table 10.1 Number of Items Missed in the Visual Search Task Used by Weintraub and Mesulam ([1987](#))

| Group | Average No. of Items Missed | |
|--|-----------------------------|------------|
| | LEFT SIDE | RIGHT SIDE |
| Patients with left-hemisphere lesions | 1.25 | 2.38 |
| Patients with right-hemisphere lesions | 17.13 | 8.00 |
| Neurologically intact control subjects | 0.56 | 0.30 |

Patients with unilateral lesions miss more items on the side of space contralateral to the lesion than on the ipsilateral side. Overall, the patients with right-hemisphere damage miss many more targets than do those with left-hemisphere damage.

Second, as you can see in [Table 10.1](#), the overall performance of patients with right-hemisphere damage was worse than the overall performance of patients with left-hemisphere damage; that is, they missed more items overall on both the left and right

sides of space. In fact, patients with right-hemisphere damage missed more items in their nonneglected hemi-space (i.e., right hemi-space) than patients with left-hemisphere damage missed in their neglected hemi-space (i.e., right hemi-space)! This piece of evidence, along with the others cited previously, suggests that the right hemisphere may exert more influence over overall attention and arousal than the left. (For a discussion of how both lateralized and nonlateralized aspects of attentional control could contribute to neglect, see Husain and Rorden, [2003](#).)

Another potential reason for the greater severity of hemineglect after right-hemisphere lesions is that the gradient of attentional allocation that we discussed earlier in this chapter differs between the hemispheres (Kinsbourne, [1993](#)). According to this model, the left hemisphere has a steep gradient, with a very strong bias for the far (i.e., right-hand) portion of space relative to ipsilateral regions of space. In contrast, the right hemisphere's bias gradient of attention (i.e., the difference in attentional allocation from contralateral to ipsilateral) may not be as drastic. Evidence consistent with the idea of hemispheric differences in the gradient of attention comes from a variety of sources. As discussed earlier, rTMS that facilitates (rather than disrupts processing) will increase attention and performance for information in right hemi-space – but it concomitantly increases errors for items in left hemi-space. This finding illustrates that the left hemisphere has a strong attentional bias to the right and, in fact, when activated, may even lead to a disruption of attention to left hemi-space. In contrast, while rTMS over the right hemisphere increases performance for items in left hemi-space, it does not increase errors in right hemi-space, suggesting that its gradient of attention is not as severe (Kim et al., [2005](#)). In addition, when attention must be distributed bilaterally (compared to only one half of space), increased activity is observed over the right but not the left inferior parietal, suggesting that the right hemisphere can distribute attention in a more bilateral manner than the left (Çiçek et al., [2007](#)).

Processing of Unattended Stimuli

Thus far, we have presented attention as a mechanism whereby the brain can choose what it wants to process from the vast array of information available. But what is the fate of unattended stimuli? Do they fall into a black hole of mental consciousness, leaving not even a trace of their existence, or are they processed but to a much lesser degree than attended stimuli? In [Chapter 6](#), we discussed the fact that patients with prosopagnosia appear to be able to extract some information about faces that they cannot recognize. Such findings provide evidence that information may be processed to some degree even if it doesn't reach consciousness. Next, we examine evidence that although patients with hemineglect appear to ignore all information on the unattended side of space, under certain conditions this information can nonetheless influence their behavior.

One of the first hints that patients with hemineglect might process information in their unattended half of space came from the case of a patient with left-sided hemineglect who was shown drawings of two houses that were identical except for flames coming out of the left side of one (Marshall and Halligan, [1988](#)). Although the patient claimed to detect no difference between the houses, when asked which house she would prefer to live in, she picked the one without flames. Although subsequent studies failed to replicate this particular finding (e.g., Bisiach and Rusconi, [1990](#)), priming studies have demonstrated that information on the left, which cannot be explicitly recognized, nonetheless influences performance.

In one study, researchers determined the speed with which neglect patients could categorize a picture in the right visual field (RVF) (their nonneglected field) as an animal or fruit. The important factor in this study was that, 400 ms earlier, a picture from either the same category or a different category was presented in the neglected field (i.e., the LVF). Responses to information in the RVF were faster when a related rather than an unrelated item was presented in the neglected field. This finding suggests that information in the neglected field was being processed to some degree, because it could influence processing of material in the nonneglected field (Berti and Rizzolatti, [1992](#)). In contrast to patients with neglect, patients with hemianopia for the LVF do not

show such priming effects, as they are truly blind to information in that portion of space (McGlinchey-Berroth et al., [1993](#); for a review of such priming studies, see Driver and Vuilleumier, [2001](#)).

Studies with fMRI have provided some insight into how brain regions might support such priming effects. These studies suggest that residual or low-level activation of brain regions allows priming but precludes conscious recognition. One case study demonstrating such a phenomenon reported a man who exhibited hemi-inattention after a right inferior parietal lobe infarction (Rees et al., [2000](#)). When shown items singly, he could identify them in each hemi-field with better than 95% accuracy, yet under conditions of bilateral simultaneous stimulation he identified only two trials as having information on both sides and said that the remaining 58 contained just a single item in the RVF. The researchers compared brain activation for the bilateral condition in which he reported seeing only the RVF item to those trials in which he truly saw only a single item in the RVF. The patient's response was the same in these two conditions even though the stimuli were distinct (bilateral as compared to unilateral). The researchers focused on activation in the visual cortex of the right hemisphere (contralateral to the neglected left field). On the trials in which the patient reported not seeing anything in the LVF, there was activation in the contralateral visual cortex, albeit somewhat reduced as compared to that observed when an item was presented solely in the LVF (and could be correctly detected by the patient) (see [Figure 10.23](#); for follow-up, see Rees et al., [2002](#)).

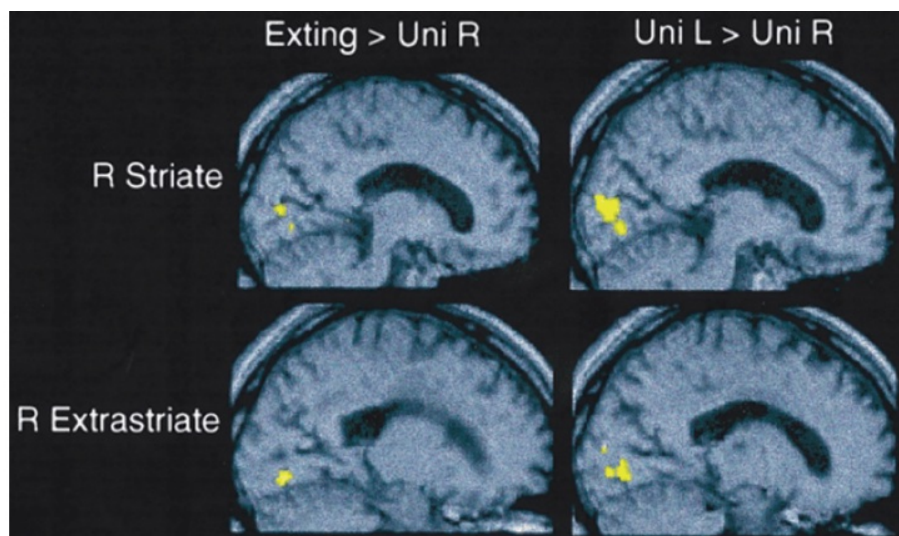


Figure 10.23 Overlap between brain regions activated when there is conscious versus unconscious perception of an item.

In this study, the individual did not consciously perceive items in the LVF under conditions of bilateral stimulation. Shown on the right side of the figure are those brain regions in striate (top row) and extrastriate (bottom row) cortex that exhibited more activity on unilateral LVF trials than RVF trials. On the left side of the figure are those brain regions in striate and extrastriate cortex that exhibited more activity to extinguished stimuli in the LVF as compared with the RVF. Notice that although they were not consciously perceived, the extinguished stimuli evoked activity in similar regions as when they were consciously perceived, although to a smaller degree.

Source: Rees et al., [2000](#). Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction, *Brain*, 123, p. 1629, fig. 2.

By permission of Oxford University Press.

ERPs provide evidence regarding the time point at which processing of neglected and nonneglected stimuli diverge. For example, a normal N170 is recorded to faces that are neglected under conditions of bilateral simultaneous stimulation (Vuilleumier et al., [2001](#)). Similarly, in response to simple visual stimuli, visual evoked potentials for the neglected hemi-field were intact up to approximately 130 ms from stimulus onset (Di Russo et al., [2008](#)). In both cases, though, components that index activation in higher-order visual areas were absent. Because neglected stimuli are processed at early stages

of the visual system, they can influence performance in subtle ways, causing the effects observed in priming studies. However, because they do not gain access to higher-order visual processing areas, they are not perceived consciously.

These studies reinforce the idea that attention serves to modulate the processing of information: Attended information is processed more fully, whereas unattended information is processed to a lesser degree. Our survey of attention has shown that this modulation occurs at many different points in time and involves many diverse regions of the cortex. This chapter has focused mainly on the modulation of activity that involves posterior regions of the brain. In [Chapter 11](#), we examine the involvement of prefrontal regions in executive aspects of attentional control, as well as other aspects of executive function.

Consciousness

As we have just discussed, the brain may still process information although we may not be fully aware of it. This leads back to an age-old question that has vexed philosophers for centuries: “What does it mean to be conscious?” and more recently “What brain systems create our sense of consciousness?” Some of the information we have already covered in this chapter provides some hints. To be conscious requires many brain regions. It requires brainstem mechanisms that keep us aroused and alert and regions of the temporoparietal junction that play a role in our awareness of items.

Not surprisingly, emerging research suggests that there is not one brain region that is the seat of consciousness, but rather consciousness is an emergent phenomenon that arises from the interaction of brain mechanisms and regions (for review see Koch et al., [2016](#)). Some representative studies will illustrate the point. In one study, researchers using MEG found that when people could consciously perceive faint stimuli in one visual field, there was an increase in the mid-frequency gamma band (54–64 Hz) activity over the occipital cortex of the contralateral hemisphere as compared to when this item was not perceived. This effect was distinct from whether or not that visual

field was attended, which was modulated instead by activity in the high-frequency gamma range (76–90 Hz) (Wyart and Tallon-Baudry, [2008](#)). Thus, the coupling of activity in occipital areas appears to correlate with conscious perception of visual stimuli.

On a broader level, scientists have used mathematical characteristics of brain activity to try to predict levels of consciousness. While much more complicated than this simplistic description, basically scientists extract information about two major aspects of brain functioning: one related to how easily information can be integrated across different regions of the brain, and the other related to how differentiated patterns of activity are across distinct brain regions. A combination of these measures is associated with conscious reports of experience across a wide range of conditions, including variations in consciousness associated with anesthetics and sleep, or between individuals who are in a minimally conscious state compared to those who have emerged from such a state (Casali et al., [2013](#)).

These findings suggest that it is the dynamics of interaction within and between brain regions that helps to define our different conscious states. Of course, any one brain metric cannot capture the complexity of conscious experience. It cannot discriminate whether an experience feels like a dream – perhaps tangible, but out of reach and a bit unreal – or whether it provides that bracing feeling of being so wonderfully alive that comes with those peak experiences in our lives when consciousness too is at its heights.

Summary

What Is “Attention”?

- Attention is the cognitive ability that allows us to deal with the inherent processing limitations of the human brain by selecting information for further processing.

- Psychologists often sort attention into four general categories: arousal, vigilance and sustained attention, selective attention, and divided attention.

Brain Structures Involved in Attention

- Alertness and arousal involve a number of brain regions. The ascending reticular activating system, the cell bodies of which reside in the brainstem, diffusely activates the cortex. A dorsal system, which sends information to the cortex via the thalamus, relies on the neurotransmitter acetylcholine. A ventral route, which sends information via the basal forebrain, relies on noradrenaline and serotonin.
- Vigilance and sustained attention are supported by cholinergic projections from the basal forebrain, the noradrenergic system, and the thalamus. Cortically, posterior regions of the right hemisphere play a role in maintaining vigilance.
- Selective attention serves to prioritize information for additional processing and can act at various points in time, from relatively soon after stimulus input to the selection of a response.
- The superior colliculus, located in the midbrain, plays an important role in automatically orienting attention to particular locations in space.
- Portions of the thalamus act as a gating mechanism for selecting or filtering incoming information.
- The parietal lobe plays an important role in selective attention. The superior parietal lobe aids in top-down control of where attention will be directed and how it will be shifted; the inferior parietal lobe aids in reorienting attention to salient perceptual information; these two streams are integrated in the intraparietal area, which is thought to weight or prioritize information to be attended.
- Medial prefrontal cortex is involved in the selection of the appropriate motor response, especially when tasks are attentionally demanding.

- Lateral prefrontal regions serve as important sources for top-down attentional control, providing the abstract category or goal that should guide attention. They send signals to posterior brain regions that act as the sites of attentional control that are actively involved in the selection process.
- Selective attention can be directed to a particular position in space; to a particular item attribute, such as color; or to a particular object. It is thought to work by biasing the competition among potential items to which attention might be directed so that some regions, items, or attributes are afforded a higher degree of priority in processing.
- In general, attention acts to increase processing in brain regions that are responsible for processing the type of information to which attention is directed, but inhibitory and suppressive influences on to-be-ignored information are also observed.
- The neural bases of divided attention, which is the ability to split one's attention between different sources of information or different tasks, remains controversial. Some research suggests that the ability to divide attention is increased when tasks rely on distinct or separate neural processors (e.g., auditory cortex, visual cortex), whereas other research suggests the existence of a central bottleneck, likely associated with operations performed by prefrontal cortex.

Network Models of Attentional Control

- Conceptually, attention is thought to be supported by a network of brain structures. One theoretical model proposes that the reticular activating system maintains vigilance and arousal, the cingulate imparts motivational significance to information (particularly when a task is difficult), the posterior parietal region provides a sensory map of the world, and frontal regions provide motor programs for moving the focus of attention.

- Another model argues for three subsystems. The first, involving the locus coeruleus, parietal cortex, and right frontal regions, supports alertness. The second, involving the superior colliculus, superior parietal region, temporoparietal junction, and frontal eye fields, allows attention to be oriented to sensory signals so as to select among them. The third subsystem, involving the basal ganglia, lateral ventral prefrontal region, and the anterior cingulate cortex, supports executive aspects of attention.
- Still other models divide regions between a dorsal attentional subsystem, involved in top-down control of attention; and a ventral subsystem, consisting of temporoparietal cortex and inferior frontal cortex of the right hemisphere, that allows attention to be directed to salient stimuli in the environment.
- The default network, consisting mainly of ventromedial prefrontal cortex, posterior cingulate and the temporal lobe, appears to be especially important when attention is directed inward to thoughts, ideas, and processes related to the self.

Hemineglect: Clinical Aspects

- In the hemineglect syndrome an individual ignores information on the side of space contralateral to a brain lesion. It is associated with damage to the ventral attentional network and connectivity between regions that form part of this network.
- The neglect is not due to sensory deficits, as the severity of neglect for the contralateral side of space does not vary with sensory modality, and individuals with a severe sensory deficit for the contralateral side of space do not exhibit neglect for that side of space.
- Neglect can be modulated by factors that draw attention to information on the neglected side of space, such as high emotional saliency, motivational factors,

and a need to process such information to gain understanding or comprehension of material.

- Theories regarding the main underlying deficit in neglect include one suggesting that patients lose the mental conception of the neglected side of space, and another suggesting competition between the attentional biases of each hemisphere to the opposite side of space.
- Treatments for neglect include guided therapy, such as visual scanning therapy to change the individual's allocation of attention; sensory stimulation of the body parts located on the neglected side of space, to make that side of space more salient; and alterations of brain activity by methods such as transcranial magnetic stimulation. In general, these therapies are aimed at altering the imbalance of activity between the hemispheres.

Hemineglect: Implications for Understanding Brain-Behavior Relationships

- Neglect illustrates that attention can be either space-based or object-based.
- The fact that neglect is more common and more severe after right-hemisphere damage suggests that the right hemisphere is more important for overall arousal and attention, and/or that the attentional gradient for the contralateral versus the ipsilateral side of space is steeper for the left hemisphere than the right.
- Material in the neglected field that cannot be identified by patients with hemineglect can nonetheless influence performance by priming certain responses, and appears to undergo early stages of processing that allow unconscious but not conscious access.

Consciousness

- Our sense of consciousness appears to derive from the integrated and potentially synchronized activity across a wide variety of brain regions.

Chapter 11

Executive Function and Higher-Order Thinking



Theoretical Perspectives

Controlled Versus Automatic Processes

Goal-Centered Processing

Multifactor Models

Goal-Directed Behaviors

Initiation of Behavior

Creation and Maintenance of a Goal or Task Set

Sequencing and Planning

Shifting Set and Modifying Strategies

Self-Monitoring and Evaluation

Inhibition

In Focus: Can You Inhibit a Memory?

Higher-Order Thinking

Abstract and Conceptual Thinking

Rules and Inference

Response to Novelty

Judgment and Decision Making

Organization of the Brain for Executive Function

A Central Role for Working Memory in Executive Function

Summary

Dr. P was a successful, middle-aged surgeon who used the financial rewards of his practice to pursue his passion for traveling and playing sports. Tragically, while he was undergoing minor facial surgery, complications caused his brain to be deprived of oxygen for a short period. The ensuing brain damage had profoundly negative consequences for his mental functioning, compromising his ability to plan, to adapt to change, and to act independently.

After the surgical mishap, standard IQ tests revealed Dr. P's intelligence to be, for the most part, in the superior range. Nonetheless, he could not handle many simple day-to-day activities and was unable to appreciate the nature of his deficits. His dysfunction was so severe that returning to work as a surgeon was impossible for him, and his brother had to be appointed Dr. P's legal guardian. As a surgeon, Dr. P had skillfully juggled many competing demands and had flexibly adjusted to master changing situations. Now, however, he was unable to carry out any but the most basic routines, and then only in a rigid, routinized manner. Furthermore, he had lost his ability to initiate actions and to plan for the future. For example, his sister-in-law had to tell him to change his clothes, and only after years of explicit rule-setting did he learn to do so on his own. He managed to work as a delivery truck driver for his brother's business, but only because his brother could structure the deliveries so that they involved minimal planning. Dr. P could not be provided with an itinerary for the deliveries of the day because he was incapable of advance planning. Rather, his brother gave him information about one delivery at a time. After each delivery, Dr. P would call in for directions to the next stop.

Dr. P appeared to be totally unaware of his situation. He seemed unconcerned about and uninterested in how he was provided with the basic

necessities of life, such as clothes, food, and lodging, and was utterly complacent about being a ward of his brother and sister-in-law. Formerly an outgoing man, he now spoke in a monotone and expressed little emotion. He did not initiate any activities or ask questions about his existence, being content to spend his free time watching television.

The case of Dr. P illustrates how brain damage can cause deficits in executive functions – which include the ability to plan actions to reach a goal, to use information flexibly, to think abstractly, and to make inferences. As illustrated by the preceding case study, difficulties in executive function can arise despite normal functioning in other domains of intellectual processing, such as those generally measured by IQ tests (retention of knowledge, vocabulary, spatial processing abilities, and so forth).

The term executive function covers many abilities, and thus it is a difficult concept to define precisely. To better understand the types of abilities that we discuss in this chapter, let's consider, by analogy, the skills and attributes required of a company executive. First, an executive must have a master plan, or a general conception of how the company should work. For example, the executive's goal may be to increase customer satisfaction, diversify markets, or raise production. He or she must be able to translate that general goal into specific actions, whether by increasing quality control, expanding the sales force, or automating factories. Second, the executive must be able to assimilate new information and use it to modify plans as the need arises; that is, the executive must be flexible and responsive to change. For example, fluctuations in the stock market or political changes in foreign governments may necessitate a modification of plans or adoption of a new course of action. Such planning ability and flexibility are not usually required of assembly-line workers, who in many cases are directed regarding what task to perform, how to do it, and when to do it. Third, an executive must keep track of multiple tasks simultaneously and understand the relationships among them, knowing which should come first and which should come second. As a result, the

executive must often prioritize both decisions and actions. For example, if limited cash flow does not allow for a simultaneous increase in the sales force and the automation of factories, priorities must be set and choices made. In a related vein, the executive must be able to assess the effect of each decision and to estimate its relative worth. Finally, an executive must be a person who projects the company image and serves as its spokesperson. As such, this job requirement calls for a certain amount of social skill and political savvy, as well as a general ability to get along with other people.

These abilities – to create a plan and follow through with it, to adapt flexibly, to sequence and prioritize, to make reasonable judgments, and to interact in a socially astute manner – are multifaceted and share many characteristics. For example, the ability to prioritize often requires creating a plan and being flexible. When prioritizing, you must have an overall plan so that you can determine which actions will best help you reach your goal. Furthermore, you must be flexible because you need to consider a variety of paths toward your goal (rather than following a rigid rule). Because of the multifaceted nature of these executive functions, more than one function usually contributes to performance of many of the complex tasks discussed in this chapter. Consequently, for executive functions, it is difficult to link one particular type of function to a specific brain region, as we did in previous chapters.

Even though executive function describes a family of related abilities, the concept has been useful to cognitive neuroscientists and neuropsychologists because it provides a way to understand a constellation of deficits. Classic work on patients with brain damage, as well as research with monkeys, has linked the frontal lobe with executive function (e.g., Fuster, [1989](#); Luria, [1966](#)). Indeed, although executive deficits can occur after posterior brain damage, they are most commonly observed after damage to frontal regions (Gläscher et al., [2012](#)). Importantly, executive deficits are often observed after damage to white-matter tracts, especially those that connect the frontal regions to other brain areas (e.g., Cristofori et al., [2015](#)). This fact indicates, as we discuss in more detail later in the chapter, that executive function most likely relies on an interacting network of brain structures.

Theoretical Perspectives

Some theorists have discussed executive function in almost philosophical terms, speaking of the frontal lobes as playing an important role in a person's ability to exert his or her will. Others have conceptualized the frontal lobe as a controller that aids in the selection of choices to produce a particular behavior, much as a controller on an assembly line might select different components to add to a car to produce the particular custom model desired by the customer. Regardless of how the issue is framed, the guidance or control of behavior toward a goal is a signature aspect of executive function, and it is equally clear that the frontal lobe plays a prominent role. Although we use the term executive function throughout the chapter, such processes are sometimes referred to as **cognitive control**, a term indicating a process in which one is guiding or controlling one's thoughts (and actions). As you will see, the concept of control is a central idea in executive function. To begin this chapter, we consider a number of proposed models of executive function, its critical elements, and its potential subcomponents.

Controlled Versus Automatic Processes

Two classic theories (Shallice, [1982](#); Stuss and Benson, [1986](#)) view the frontal lobes as playing an important role in executive function because they are critical for controlled compared to automatic processing. Shallice ([1982](#)) suggested that a two-component system influences the choice of behavior. One part, **contention scheduling**, is a cognitive system that enables relatively automatic processing, which has been learned over time. Stimuli or situations become linked to actions, routines, or processing schemes, and then groups of these routines become linked to one another. In this manner, a single stimulus may result in a relatively automatic string of actions, referred to as a schema. For example, seeing a red light when you are driving automatically causes a series of actions: taking your foot off the gas, depressing the brake pedal, determining

how hard the pedal must be pushed to stop in time, deciding where to stop, and so forth. Once any action is initiated by this system, it continues to be active until inhibited by a mutually incompatible process.

The second part of this model, the [supervisory attentional system](#), is the cognitive system required to effortfully direct attention and guide action through decision processes. It is active only in certain situations: when no preexisting processing schemes are available, as in novel situations; when the task is technically difficult; when problem solving is required; and when certain typical response tendencies must be overridden. Although the supervisory attentional system was initially thought of as a unitary system, more recent versions of this model assume that it has some subcomponents, such as those that activate certain schemas, inhibit others, and monitor the levels across schemas (Shallice and Burgess, [1996](#)).

According to this theory, frontal lobe damage disables the supervisory attentional system and thereby leaves actions to be governed totally by contention scheduling, a situation that has a number of implications. First, it implies that patients with frontal lobe damage will show few deficits in fairly routine situations in which the appropriate response is evoked by a stimulus in a simple and obvious way. So, for example, their performance is the same as that of neurologically intact people on many tests administered in a standard IQ battery, because these tasks, such as providing a definition of a word, are often familiar and well practiced. However, when a situation is novel or requires flexibility, people with frontal lobe damage fail to respond appropriately, because no schema is available in contention scheduling.

Second, these patients will appear to be disinhibited, with an inability to control behavior or urges, including those in the social realm (e.g., saying exactly what they think even though it might not be appropriate) (Knutson et al., [2015](#)). Sometimes their behavior can be triggered by stimuli in the environment. For example, upon seeing a pen on a desk, they may pick it up and begin to write. This action occurs because over time one learns that a desk with writing implements on it is linked to certain actions – picking up the implements and using them to write – and when the supervisory

attentional system is lost, the typical schemes of contention scheduling are invoked automatically. Some theorists have referred to this behavior as an [environmental dependency syndrome](#) (e.g., Lhermitte, [1983](#); Lhermitte et al., [1986](#)). It is as if these patients' actions are impelled or obligated by their physical and social environment (see some examples of such behaviors in [Figure 11.1](#)).



Figure 11.1 Two examples of the environmental dependency syndrome exhibited by patients with frontal lobe damage when they visited their physician's home.

(A) The man, upon seeing two pictures lying on the floor, picked up a hammer and nails and hung the pictures on the wall. (B) The woman, upon seeing the dishes in the kitchen, began to wash them.

Source: "Human Autonomy and the Frontal Lobes; Part II. Patient Behavior in Complex and Social Situations. The 'Environmental Dependency Syndrome'" by F. Lhermitte, [1986](#). *Annals of Neurology*, 19 (4), pp. 339, 340. By permission of John Wiley & Sons, Inc.

Notably, this environmental dependency syndrome will often be expressed in different forms depending on an individual's personal history prior to injury. Consider the following cases of two patients with executive dysfunction, each of whom was

attending the same buffet dinner (Lhermitte, [1986](#)). One patient, a man from an upper-class background, behaved like a guest expecting to be served. In contrast, the other patient, a woman who had been a modest housekeeper for most of her life, immediately began serving the other guests. The types of behavior that had become automatic, and therefore controlled by contention scheduling, differed for these two individuals because of their different life experiences.

Third, this theory explains why patients with frontal lobe damage often exhibit [perseveration](#), which is the behavior of repeating the same action (or thought) over and over again (Kleinman et al., [2013](#)). Once a strong trigger activates a scheme or an action, this process will continue to be invoked until some incompatible process is activated. Without the supervisory attentional system, iterative actions triggered by contention scheduling are difficult to interrupt, resulting in perseveration.

Like Shallice's theory, the theory of Stuss and Benson ([1986](#)) suggests that the frontal lobes are especially important in regulating behavior in nonroutine situations or in situations in which behavior must be carefully constrained. Their model links the degree of control to particular neural substrates in a hierarchical manner. At the lowest level, sensory information and simple tasks are processed by posterior regions of the brain in a relatively automatic manner that varies little from day to day. Processing of such information is thought to be difficult to control consciously. The next level of control is associated with the executive, or supervisory, functions of the frontal lobe. At this level, lower-level sensory information is adjusted so that behavior can be guided toward a goal. Control of behavior is effortful and slow and requires conscious control. The highest level of control involves self-reflection and metacognition. Self-reflection allows an individual to have self-awareness and to understand the relationship of the self to the environment; [metacognition](#) is the ability to reflect upon a cognitive process. Such a control level permits one to develop an abstract mental representation of the world and the way one chooses to act in the world. This process is considered to be under the control of the prefrontal cortex.

This model explains deficits in executive function by arguing that the organization of behavior is one of the main functions of frontal regions. It explains deficits in dealing with novelty and lack of cognitive flexibility because the frontal lobes are assumed to be important for nonautomatic behavior. The inability to guide behavior and the undue influence of the environment occur because, without the frontal lobe, responses to sensory stimuli are automatic. Finally, the inability to self-criticize or self-monitor could be explained by this model as resulting from prefrontal region damage, which would leave patients devoid of any ability to reflect upon themselves or the processes in which they become engaged.

Goal-Centered Processing

Other approaches to understanding executive control emphasize that it allows one to guide behavior toward a goal. Some models draw from work in artificial intelligence, which has investigated what type of computational structures are required to reach a goal. These artificial intelligence approaches suggest that reaching a goal requires the creation of a hierarchy of simpler and more solvable subgoals. Then for each subgoal, the steps required to achieve those subgoals must be determined and specified. It has been argued that frontal lobe damage disrupts the ability to create such a hierarchical goal list (Duncan, [1986](#)).

From this viewpoint, the frontal lobes support executive function in a relatively undifferentiated manner because the same set of brain regions becomes activated across a wide variety of tasks (Duncan and Owen, [2000](#)). More recent conceptualization of this model argues, in fact, that there is a Multiple Demand System (Duncan, [2013](#)) that is utilized for executive processing across many different domains including language, memory and math (Fedorenko et al., [2013](#)). While the frontal lobes are part of this Multiple Demand System, other brain regions including the portions of the parietal lobe, the basal ganglia, and cerebellum are part of it as well.

Other models emphasize the role of the prefrontal cortex in providing a bias signal to other brain systems depending on the current context. Similar to the ideas we just

discussed, this system is “all-purpose” in that it guides activity in the rest of the cortex across a range of systems from sensory processing to memory, emotion, and response output, so as to enable and meet goals (Miller and Cohen, [2001](#)). As an analogy, you can consider the role of frontal cortex as akin to setting switches on a series of railroad tracks to ensure that a train arrives at the correct destination. The correct destination, however, will vary depending on the context. For example, an individual might usually cook oatmeal in a pot of boiling water for breakfast in the morning, but if the goal is to make oatmeal cookies, cooking oatmeal in this manner would be inappropriate, and doing so would derail the train and keep it from reaching its destination.

This model also emphasizes the need for sustained maintenance of the goal while the task is being performed, to aid in guiding the train at each of multiple junctions to the correct destination. Keeping in mind that the goal is to make cookies will preclude dropping the oatmeal into boiling water. Without sensitivity to context and the ability to modulate behavior based on goals, people will perseverate and engage in routine acts that may not be suited for the particular task at hand. Furthermore, their behavior will appear disorganized and off the mark.

Multifactor Models

Unlike the models we just discussed that assume executive control works in a relatively unitary manner, other models argue that executive function may consist of separable facets or factors. One model, called the unity and diversity model (Miyake et al., [2000](#); Miyake and Friedman, [2012](#)), argues that executive function consists of one common factor required for all executive function, as well as more specialized functions that are only required in specific situations. The common factor thought to be required whenever executive function is invoked is the ability to maintain task goals (especially in the face of distraction). This idea is in good accord with the models we have just discussed that emphasize the importance of executive function in enabling goal-directed behavior.

In addition to this general factor, the model proposes that there are two other separable and more specific aspects of executive function that are only required under

certain situations or conditions. These two factors represent the “diversity” aspect of the model. One of these specialized factors is the ability to switch between tasks or subgoals so as to guide behavior appropriately. As a commonplace example, think about efficiently making an omelet. You need to heat the skillet, warm the butter, and sauté the ingredients such as onions and pepper. But as they are cooking, you need to switch to beating the eggs. And then you need to switch back to putting the eggs in the skillet. The other specialized factor is the ability to update information being held in working memory. This ability is especially important when new and novel information is encountered and must be incorporated into ongoing processing or when a subgoal has been reached and the system must be “reset” for the next subgoal. Currently, the brain regions that might be critically or uniquely supporting each of these three components of executive function is an area of active investigation.

Other researchers, drawing on the pattern of behavioral impairment observed in patients with brain damage, have suggested that three different and separable basic subprocesses underlie executive function and that each is supported by a different region of prefrontal cortex (Stuss and Alexander, [2007](#); Stuss, [2011](#)). One subprocess drives initiating and sustaining a response, especially when such behavior is not triggered or driven by environmental stimuli. It is posited to rely on medial frontal regions. A second subprocess involves task-setting, which enables a task to be chosen and provides the steps required to perform the task. It has been proposed to rely on left lateral regions of the frontal lobe. The final subprocess is monitoring, which is the checking of behavior over time to ensure that it is being produced correctly, and to make any adjustment of behavior that might be required. This subprocess is thought to rely on right lateral regions of prefrontal cortex.

The reason that we discuss these models is not so much to adjudicate between them, but rather to provide some sense of the multiplicity of viewpoints that have been brought to bear in trying to understand executive function. It is not surprising that there is quite a diversity of viewpoints as executive function is probably one of the most complex abilities performed by the human brain. However, regardless of the specifics of these

models, what we can derive from them is that executive function can be considered a process that allows behavior to be effortfully guided to a goal, especially in nonroutine behaviors (Banich, [2009](#)).

In the [next section](#), we attempt to understand executive function a bit more by breaking it down into meaningful subcomponents. Because goal-directed behavior is such a central aspect of executive function, we organize our discussion by the variety of subprocesses that are invoked when working toward a goal. Some of these subprocesses, such as the ability to create an overall goal, have already been mentioned. However, there are other subprocesses, such as monitoring and evaluating one's behavior, that have not been mentioned in detail. In the [next section](#), we consider them as well.

Goal-Directed Behaviors

Guiding behavior toward a goal is not a simple function, but rather is multifaceted. As we will learn shortly, the loss of any facet of goal-oriented behavior can cause the entire plan to be derailed. Consider the multiple aspects of the “simple” task of making yourself a peanut butter and jelly sandwich. First, the ultimate goal must be kept in mind throughout the procedure. For example, even though you are in the kitchen, which contains many other foods, you need to keep focused on the peanut butter and jelly. You must also keep this goal in mind even though subgoals must be met along the way. For example, although locating the bread may be the first step in making the sandwich, after attaining that subgoal, you must remember the ultimate goal and switch to finding the peanut butter or the jelly. Second, attaining the goal requires flexibility and adaptability. If you remember that the jelly is on the top shelf of the refrigerator but do not find it there, you must devise an alternative strategy, such as searching the other shelves or looking among the racks on the door. Third, to reach the ultimate goal, you must distinguish the completed portions of the task from those yet to be attained. Thus, after locating the jelly, you must remember not to turn your attention to finding some pieces of

bread (because you already did that). Fourth, you must evaluate the actions that will best help you to reach the goal. For example, you must realize that although a fork is in front of you, it is not the utensil best suited for making your sandwich. Instead, you must decide that the best course of action is to search through the silverware drawer for a knife. Finally, actions must be sequenced toward the goal. Only after you find the ingredients – the bread, the peanut butter, and the jelly – as well as the necessary utensil, the knife, do you proceed to make the sandwich. Although you probably do not think about it much when you go to the kitchen to fix yourself a sandwich, you can now appreciate how complicated that action really is!

In describing the construction of a peanut butter and jelly sandwich, we listed a number of skills: staying on task; [sequencing](#), or planning, information; modifying strategies; using knowledge in your plans; and monitoring your actions. We now examine these various subprocesses involved in goal-oriented behavior and examine the neural structures that support these functions. At the outset, we should point out that these functions are not likely to rely on only one particular region of the frontal lobe. This fact is reflected in the organization of this chapter – we organize it by subprocesses and not by brain region. Rather, many of these functions rely on overlapping portions of the frontal lobe. While reading this chapter, you may want to refer to [Figure 11.2](#) to help you stay oriented to the different regions under discussion. Moreover, executive function is likely to be supported not only by the pattern of activity within portions of the frontal lobe, but also by the degree to which frontal cortex influences or interacts with other regions of the brain.

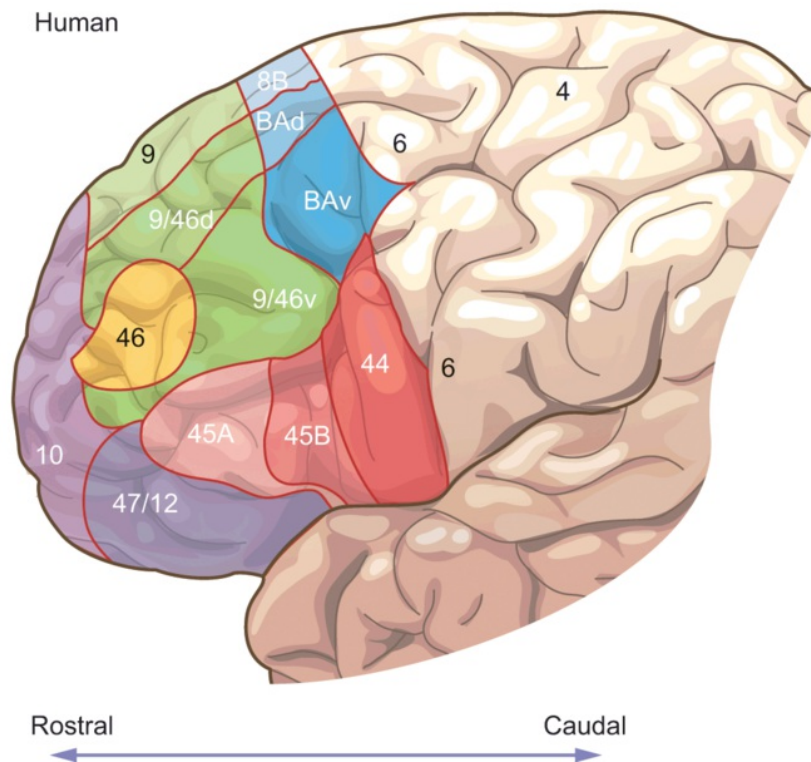


Figure 11.2 The human lateral prefrontal cortex.

Brodman regions of the lateral prefrontal cortex.

(from Badre and D'Esposito, [2009](#))

Initiation of Behavior

One difficulty often observed in patients with executive dysfunction is referred to as **psychological inertia** (Lezak et al., [2012](#); Luria, [1966](#)). In physics, inertia is the tendency of a body at rest to stay at rest or a body in motion to stay in motion unless acted upon by an outside force; it is resistance or disinclination to motion, action, or change. Patients with executive dysfunction are poor at starting an action or a behavior, but once engaged in it, they have great difficulty stopping it. Here we focus on the initiation of behaviors; later in this section we discuss the interruption or cessation of behavior.

As illustrated by the vignette at the beginning of this chapter, difficulties in overcoming psychological inertia can permeate much of the existence of people with prefrontal damage. Dr. P took no initiative in terms of his personal hygiene or his day-

to-day activities, did not inquire about either the state of events in his life or those in the world, and tended not to speak unless spoken to. In fact, patients with left frontal lobe damage often exhibit a marked reduction in spontaneous speech (Milner, [1971](#)). Moreover, higher scores on clinical scales that measure difficulties in initiation and perseveration are associated with frontal lobe damage (Mok et al., [2008](#)).

As mentioned earlier, the ability to initiate and sustain responding is one of the three major subcomponents of executive function proposed by Stuss and Alexander ([2007](#)). They observed that patients with damage to medial frontal regions, including the supplementary motor area and anterior cingulate, show differential difficulty in responding quickly compared to patients with damage in other frontal regions. You should not find this association all that surprising given that we learned in [Chapter 4](#) that these two medial portions of the frontal lobe are involved in motor planning and selection. Converging evidence comes from patients who have dementia due to frontotemporal degeneration (a syndrome that we discuss more in [Chapter 16](#)). In these patients, the larger the atrophy in gray matter in the cingulate, the greater is their difficulty in initiating behavior on a computerized task (Massimo et al., [2015](#)).

However, the difficulties go beyond just responding. A waitress, explaining why she had lost her job after frontal lobe surgery, said, “You have to have a ‘push’ to wait on several tables at once, and I just didn’t have it anymore” (Malmo, 1948, p. 542, cited in Duncan, [1986](#)). Growing evidence implies that regions of the medial prefrontal cortex are involved in determining how much “effort” will be exerted to reach a goal. For example, rats who have lesions to the anterior cingulate do not tend to engage in actions that although effortful would lead to high rewards (Walton et al., [2003](#)). Activity in cells in the SMA and pre-SMA of monkeys that predict the initiation of movement tend to do so mainly under the context of an expectation of reward (Scangos and Stuphorn, [2010](#)). Finally, single-cell recordings in macaques suggest that ACC cells appear to calculate a cost-benefit analysis, with their firing rate dependent on the interaction of two factors: how large a potential reward is and how much effort is required to raise a bar to

receive that potential reward (Hosokawa et al., [2013](#)). As such, research with monkeys suggests that the ACC is not only involved in performing goal-oriented movement, but also in determining the amount of effort that is required to reach that goal.

Human neuroimaging evidence also indicates that the anterior cingulate integrates information about effort and reward (Klein-Flügge et al., [2016](#)). In one study, individuals decided how much physical effort, as measured by the force of a squeeze, they were willing to exert to get a reward. As more effort was needed to get a reward, there was increased activation in dorsal regions of the anterior cingulate cortex and the pre-SMA (see [Figure 11.3](#)). This evidence suggests that one potential reason patients with medial prefrontal damage may have difficulty in initiating behavior is because the goal or potential outcome does not seem worth the effort.

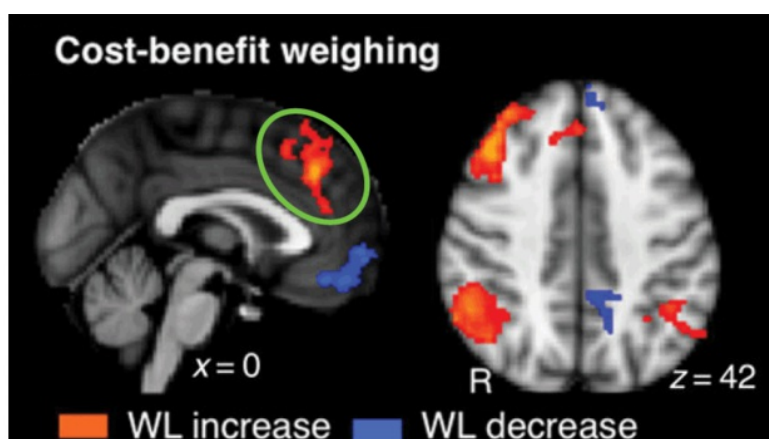


Figure 11.3 Regions of the anterior cingulate that are involved in calculating a cost-benefit analysis, that is, the degree of effort required to obtain an outcome. Areas shown in red are those regions of the brain that show increases in activation with the degree of reward relative to effort (cost-benefit weight loading – WL). Notice the extensive activation in the anterior cingulate and pre-SMA (circled in green).

(from Bonnelle et al., [2016](#))

Yet as we have mentioned previously, executive function tends to be influenced by the interaction between brain regions. This is also the case with regards to the ACC. In

one study, researchers determined, via a self-report questionnaire, how much a person exhibits behavioral apathy, which is the lack of motivation to initiate behavior or respond to environmental stimuli. More apathetic people tend to disagree with statements like “I don’t like to laze around,” and “When I decide to do something, I am motivated to see it through to the end”. These individuals also show less connectivity between the ACC and pre-SMA both in terms of co-activation of function and also in terms of the integrity of white matter that connects these areas (Bonnelle et al., [2016](#)). Therefore, the ability to initiate action, especially under effortful condition, appears to involve dorsal regions of the medial prefrontal cortex as well as its connections to other frontal regions.

Creation and Maintenance of a Goal or Task Set

One of the most basic prerequisites for meeting a goal is the ability to stay on task. Patients with frontal lobe damage are notorious for “wandering off task.” For example, if asked to draw a square, persons with frontal lobe damage may start drawing a square but then begin to incorporate words from a nearby conversation into the drawing without seeming to realize or care that such actions are incompatible with (and irrelevant to) what they set out to do (Luria, [1966](#)). This behavior contrasts with behavior of people with nonfrontal lesions in similar situations. For example, a person whose visuospatial abilities have been compromised by a right posterior lesion will have difficulty drawing the square, but will nonetheless continue in the attempt rather than engaging in some irrelevant activity. In fact, task-setting is considered one of the core subcomponents of executive function, according to some models (e.g., Stuss and Alexander, [2007](#)). Task-setting has been associated with lateral prefrontal regions of the left hemisphere on the basis of behavioral difficulty in this realm in patients with damage to this area.

Consistent with such a viewpoint, neuroimaging data suggest that dorsolateral prefrontal regions aid in creating and maintaining an [attentional set](#), which can be

thought of as the process that designates which information is task-relevant. One way in which this issue has been investigated is to determine which regions become active in response to a cue that designates what attentional set should be employed. For example, in one study employing the Stroop task, a cue appeared 1.5 seconds before the actual stimulus. This cue indicated whether the person should identify the color named by the word or the font color in which the word was printed. Lateral prefrontal cortex became active during the cue period prior to presentation of the stimulus. Moreover, the greater the degree of activation in left lateral prefrontal cortex after the task cue, the less a competing color name slowed responses, suggesting that this region helps to impose the correct attentional or task set (MacDonald et al., [2000](#)).

Another way to investigate the neural underpinnings of maintaining an attentional set is to determine which regions become activated when it is difficult to maintain a task set. Consider, once again, the Stroop task in which the person is told to identify the ink color in which a word is printed while ignoring what the word means. In this case, one must impose an attentional set for determining ink color rather than getting distracted by reading the word, which is hard to do because we read words automatically. Under such demanding conditions, activation is observed in lateral prefrontal regions. Conversely, if attention should be paid to the word rather than the color, no increased lateral prefrontal activation is noted. Moreover, the difficulty of imposing the task set appears to be critical. For example, if the task is altered so that it is easier to identify the color than to identify another dimension of the stimulus, such as its shape, then dorsolateral prefrontal activity is observed when attention is paid to shape, but not to color. Thus, it appears that prefrontal areas help us stay on task, especially when irrelevant information is particularly distracting, regardless of the nature of the distracting information (Banich et al., [2000](#)).

Reinforcing these findings, researchers have also found that activity in these lateral prefrontal regions depends on how large the change in attention set must be from one trial to the other. As shown in [Figure 11.4](#), lateral regions of prefrontal cortex (as well as some medial regions) are active during a cue period indicating what dimension

should be used to guide responses. Moreover, the greater the difference in the nature of the task set from the prior trial, the greater the activity in these regions (Slagter et al., [2006](#)). However, other neuroimaging data implicate different regions other than lateral prefrontal cortex in maintaining an attentional set.

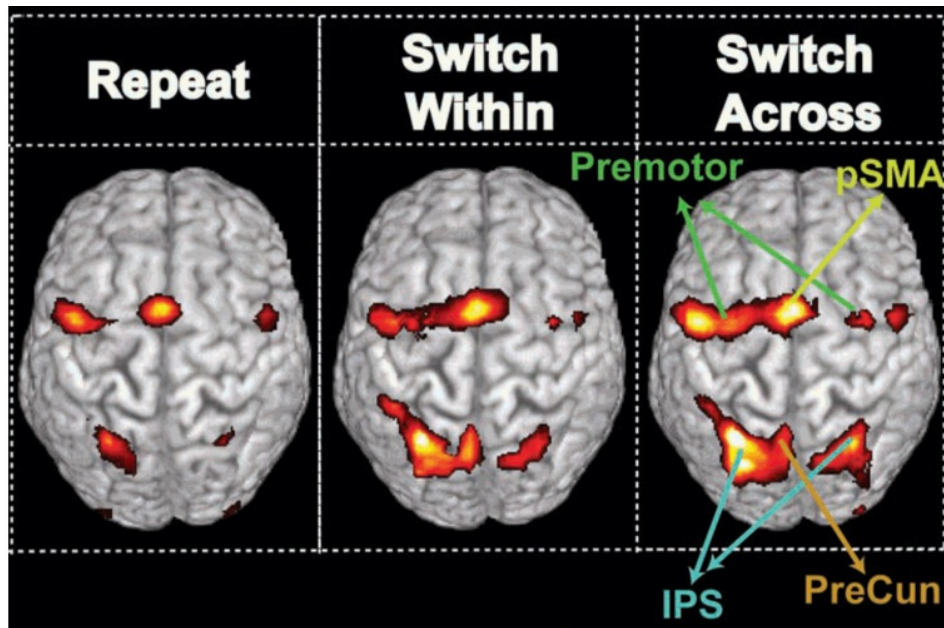


Figure 11.4 Evidence that prefrontal areas are involved in creating an attentional set for the task to be performed.

Shown here is activity during a cue period (before any stimulus is presented on the screen) when individuals had to make a decision about the orientation of one of two rectangles. The cue identified the rectangle on which a response should be based. In the repeat trials, the critical dimension was the same as for the previous trial (e.g., respond to the blue rectangle). In the switch within trials, the critical dimension was a different specific attribute (e.g., yellow) but within the same category (color). Finally, in the switch across trials, the attribute switched to a new category (e.g., location, left or right). Two important findings are shown above. First, during the cue period, there is activity in posterior regions of prefrontal cortex, including portions of the premotor area and pre-SMA, indicating that these regions are involved in creating a top-down attentional set for the task-relevant feature (i.e., color or location). Second, the greater the reconfiguration of this task set from one trial to another (greatest on switch across, intermediate on switch within, and least on repeat), the greater the activity within these regions.

(from Slagter et al., [2006](#))

Some researchers have argued that a brain region involved in maintaining an attentional set should be characterized by a specific profile of activity (Dosenbach et

al., [2006](#)). More specifically, activity in these regions should (a) rise when the task set first needs to be implemented, (b) be sustained for as long as the task is being performed, and (c) should show periodic increases in activity after errors so as to reimpose the task set to preclude further errors. The brain regions that show such a profile do not include dorsolateral prefrontal cortex, but rather the anterior cingulate and the frontal operculum and anterior insula (a brain region sandwiched between the ventral frontal lobe and temporal lobe) (see [Figure 11.5](#)). Yet, this sustained activation might reflect some other process rather than the imposition of a task set, such as the need to stay alert and aroused during the task (Braver and Barch, [2006](#)). Thus, the exact role of these additional regions in creating and maintaining a task set has yet to be resolved.

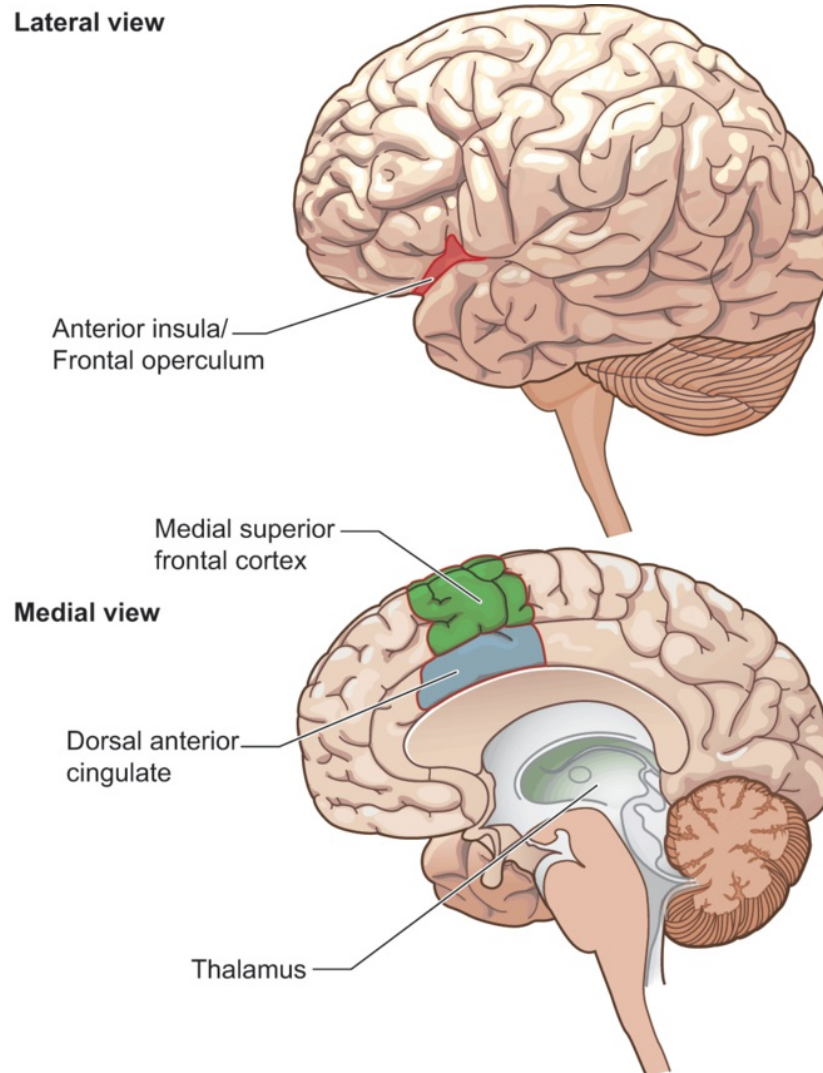


Figure 11.5 The location of other brain regions that have been implicated in imposing a top-down attentional set.

According to some models, a cingulo-opercular network involving medial superior frontal cortex (shown in green), cingulate regions (shown in blue) as well as the operculum and anterior insula (shown in red) create and maintain an attentional set. They become active when an attentional set needs to be initiated, remain active during the task, and increase in activation when errors are made.

One potential resolution of this controversy is to suggest that lateral prefrontal regions create the overall task set (e.g., pay attention to ink color), while medial prefrontal regions create a task set for appropriate responses (e.g., get ready for one of your fingers to press a button) (Ruge et al., [2009](#)). In fact, fascinating research suggests

that by recording and analyzing the pattern of activity over both lateral and medial prefrontal regions using multi-voxel pattern analysis, scientists can predict which of a number of tasks a person is about to perform (Haynes et al., [2007](#))!

But what happens if a person needs to maintain more than one task set at time? For example, you might be fixing dinner when the telephone rings. Here you need to keep both tasks – making dinner and answering the phone – in mind while performing the components of each. Research has implicated frontopolar cortex (BA 10) in such behaviors. This area likely integrates the outputs of processing for two or more separate operations in service of a higher goal (Ramnani and Owen, [2004](#)). For example, it may help to process subgoals (e.g., get the pasta cooking; get the tomato sauce cooking) and then integrate information so as to determine if goals are being met (e.g., if the pasta is cooked and the sauce thick enough, then dinner is ready) (Braver and Bongiolatti, [2002](#); Kim et al., [2015](#)).

In fact, individuals with damage to frontopolar cortex have specific difficulty in managing subgoals, with a greater extent of damage predicting greater impairment in the management of multiple goals (Dreher et al., [2008](#)). Other evidence from patients with damage to this region suggests that it may manage subgoals by serving as a controller that coordinates activity in other brain regions. Supporting this idea, patients with damage to rostral prefrontal cortex show less coordinated activity across the integrated set of frontal and posterior brain regions that typically becomes active in neurologically normal individuals in response to a cue indicating what type of decision should be made on a subsequently presented stimulus (Rowe et al., [2007](#)).

Still another way to investigate the neural bases of an attentional set is to compare brain activity when people choose what task they will perform, compared to when they are instructed what task to perform. More activity is observed in dorsolateral prefrontal cortex (DLPFC) (Bengtsson et al., [2009](#)) and in portions of the anterior cingulate cortex (e.g., Forstmann et al., [2006](#); Demanet et al., [2013](#)) when people make the selection themselves, compared to when they are told what task to perform. These findings are consistent with prior evidence of both these regions in creating and/or implementing a

task set. Other studies have reported activity in frontopolar regions as well (Orr and Banich, 2014) consistent with the idea that this region is involved in selecting which of the potential task sets is to be employed (see Figure 11.6). In addition, MVPA over medial orbitofrontal regions can predict, prior to a participant's overt response, whether the person will voluntarily decide to perform an addition or subtraction task (Soon et al., 2013).

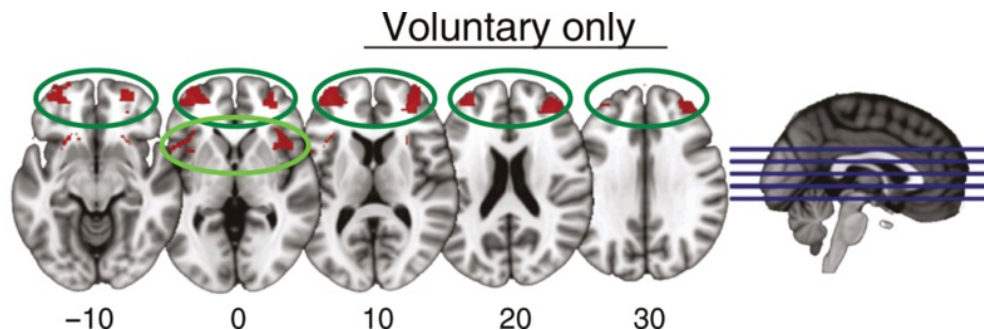


Figure 11.6 Areas of cortex that become active when people have to voluntarily select between two potential task sets.

Circled in dark green are frontopolar regions and circled in light green are insula/opercular areas that become more active when individuals choose which task to perform (a decision about the numerical value vs. a decision about the physical size of a number) rather than being instructed which task to do.

In summary, creating and maintaining a task set is likely to involve interactions between frontopolar, lateral, and medial prefrontal regions. The relative contributions of each of these regions is likely to vary depending on task demands. For example, the contribution of frontopolar regions may predominate if there are multiple subgoals to be coordinated, lateral regions may predominate when the task set is hard to maintain because of distracting information, and medial prefrontal regions may predominate when the array of potential motoric responses is paramount.

Sequencing and Planning

One of the basic processes involved in reaching a goal is determining what steps to take to attain the goal, and the order in which those steps must be taken. Little in life can be accomplished in just one step, and even the most basic functions, such as feeding oneself, require multiple steps. In this section, we review evidence that sequencing and planning abilities rely mainly on frontal regions. As discussed in [Chapter 4](#), anterior regions of the brain are important for sequencing movements. Here we learn that they are important for the sequencing of thoughts as well.

A basic ability required for sequencing behavior is to know what comes before and what comes after. Evidence from single-cell recordings in monkeys suggests that there are neurons in prefrontal cortex that distinguish between those tasks that have just been accomplished versus those tasks that are about to be performed. Extrapolating to people, disruptions to mechanisms that code for tasks or goals yet to be accomplished could lead to errors of omission, in which case a goal is forgotten or not accomplished. Disruptions to mechanisms that code for previously completed tasks or goals could lead to perservation (Genovesio et al., [2006](#)).

Initial evidence regarding the neural underpinnings of sequencing and planning in humans came from studies of patients with brain damage. Compared with people who have brain damage in other cortical regions, people with frontal lobe damage have difficulty in this arena (Milner, [1982](#)). In one task, participants view an inspection series of items, such as line drawings, one by one. They are then shown cards on which two items appear. If they must determine which of the two items was presented in the inspection series, patients with frontal lobe damage have no difficulty. However, they have difficulty in remembering the sequence in which information was presented regardless of whether they are passively watching the sequence of events or if they control the order of events.

In a paradigm known as the [self-ordered pointing task](#), individuals are shown an array of items, anywhere from six to twelve, all of which are from the same category (e.g., abstract designs or high-imagery words). Assume for the moment that we are using a six-item array. On each trial, the participant views six sheets of paper presented

sequentially. Although each sheet contains all six items (arranged in a two-by-three matrix), the position of each item in the array varies from sheet to sheet. On each sheet, the participant must point to an item that was not previously chosen. Because a given item appears in a different location on each page, the person must keep track of which items were previously selected (see [Figure 11.7](#); Petrides and Milner, [1982](#)). Deficits on this task are observed after frontal lobe damage. Subsequent work revealed that damage to lateral regions of prefrontal cortex disrupts recency judgments more than damage to other regions of the frontal cortex does (Milner et al., [1991](#)). Corroborating these findings, neurologically normal individuals show greater activation in lateral prefrontal regions for recency judgments than determining whether an item has been viewed previously (i.e., recognition memory) (Amiez and Petrides, [2007](#)).

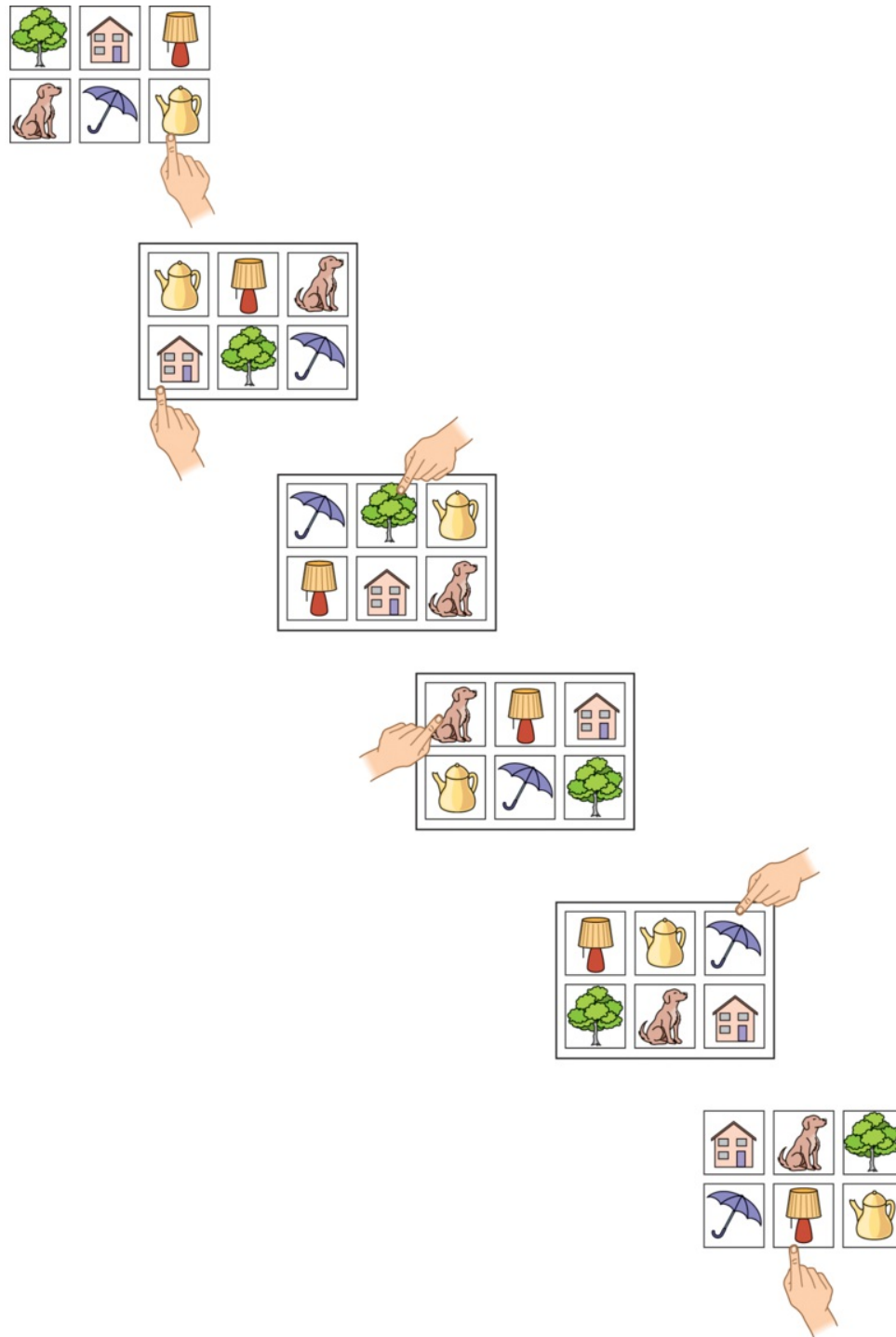


Figure 11.7 An example of a task that requires sequencing and on which individuals with frontal lobe damage exhibit difficulty.

Shown here is an example of correct performance on a six-item self-ordered pointing task. The person must point to a different item on each page, and the position of each picture varies from page to page. To correctly perform the task, the person must remember what they have just recently selected.

Dorsolateral prefrontal regions may be important in these tasks because these regions help to support executive processes that act on information being maintained in working memory. As you may remember from [Chapter 9](#), working memory is used to keep information on-line to control behavior and acts as a sort of mental scratch pad during everyday actions. In the self-ordered pointing task, executive processes are required to differentiate which items in working memory have already been pointed to and which remain to be selected. Likewise, the recency judgment task requires an individual not just to maintain information, but specifically to determine the relative position of two items vis-à-vis the order in which they appeared.

Other frontal regions, in addition to the DLPFC, also appear to contribute to sequencing and planning. As we discussed [Chapter 8](#), ventral regions of lateral prefrontal cortex (i.e., Broca's area) appear to play an important role in aspects of language that involve sequencing, such as syntax. Which words come first in a sentence and which come later influences meaning. For example, the word order in the sentence "The dog bit the rat" conveys a different meaning than the word order in the sentence "The rat bit the dog" (see page [230](#)). In fact, patients with damage to this region (BA 44/BA 6) show difficulty in reproducing the order of a sequence of visual items by pressing a button associated with each item (Thothathiri et al., [2012](#)). Further, this region shows specific activation in a parallel neuroimaging study with neurologically intact people when sequencing demands were high because the information to sequence was shown concurrently instead of sequentially (Thothathiri and Rattinger, [2015](#)).

Other studies show that Broca's area responds to sequential processing demands, regardless of whether information is linguistic or musical. In one study, participants heard a series of three notes or three syllables. In the conditions of interest, participants had to decide if a subsequently heard stimuli was a reordering of the initial sequence, such as the same three items but in backward order. The control condition was just deciding if the initial and subsequent triads were identical. More activity was observed

in Broca's area when the information had to be re-sequenced rather than when an identity match was required (Gelfand and Bookheimer, [2003](#)).

Thus far, we have discussed sequencing abilities from two perspectives: being able to appreciate the sequence in which events occur and being able to generate sequential behavior. Another important aspect of sequencing behavior is the ability to choose which sequence or strategy best allows a goal to be attained. Compared to individuals who have damage to other brain regions, patients with frontal lobe damage are less likely to report that they use strategies, and when they do use a strategy, it tends to be ill-defined or invoked inconsistently.

One task designed specifically to examine the ability to use strategies to sequence action is the [Tower of London task](#) (Shallice, [1982](#)), shown in [Figure 11.8](#). The apparatus for the task consists of three prongs of varying height and three colored balls with holes that allow them to be placed on the prongs. The first prong can hold three balls, the second can hold two, and the last can hold only one. The task requires the individual to move the balls, one at a time, from an initial position to a target configuration in as few moves as possible while keeping in mind the constraints imposed by the height of each prong. The puzzles range in difficulty, with some that can be solved in just a few moves (e.g., 3) and others taking more moves (e.g., 7).

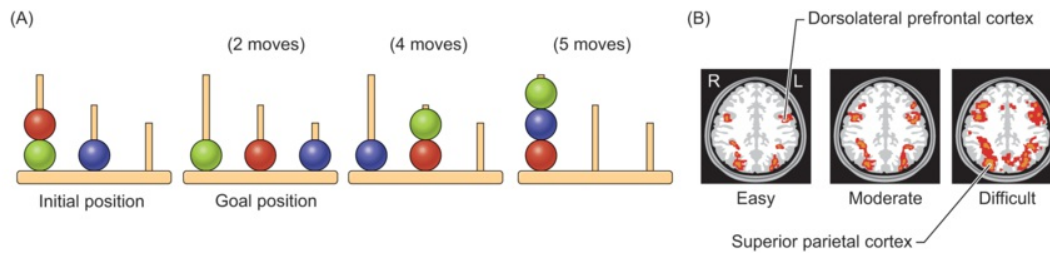


Figure 11.8 The Tower of London task, which is used to examine planning and sequencing abilities.

(A) In this task, the person is shown an initial position and a goal position to which the balls must be moved, one at a time, in as few moves as possible. The minimum number of moves required to reach each goal is noted. (B) Increasing activation of prefrontal regions as task complexity increases in the Tower of London task.

(from Newman et al., [2003](#))

Researchers have attempted to determine whether performance on the Tower of London task can be predicted by basic underlying abilities, such as verbal or spatial working memory or general intelligence. In fact, performance on the more difficult puzzles cannot be predicted by any of these factors, suggesting that the task is a reasonably specific test of planning and sequencing (Unterrainer et al., [2004](#); Debelak et al., [2016](#)).

Patients with frontal lobe damage are both inefficient and ineffective at performing the Tower of London task. They are inefficient because they take many moves to reach the end position and are ineffective because they engage in behaviors that are aimless rather than directed toward the goal. A meta-analysis across a variety of neuroimaging studies suggests that dorsolateral prefrontal regions may play a particularly important role in this task (Nitschke et al., [2017](#)). One piece of evidence supporting this viewpoint is that as the difficulty of the puzzle increases, so does activation in DLPFC (van den Heuvel et al., [2003](#)).

Currently it is not clear whether left dorsolateral prefrontal regions are specifically important or whether DLPFC bilaterally plays a role. At least some evidence suggests a particularly strong role for left DLPFC. Some evidence comes from studies using

transcranial direct current stimulation (tDCS), which as we learned in [Chapter 3](#) is a method in which electrical activity is used to modify brain activation. Compared to sham activation, tDCS over the left dorsolateral prefrontal cortex leads to better performance on the Tower of London test, as measured both by accuracy and reaction time (RT), right after stimulation and 6–12 months later (Dockery et al., [2009](#)). However, suggesting bilateral involvement of DLPFC, performance on the Tower of London task can be influenced by tDCS either over the left dorsolateral prefrontal cortex or over the right dorsolateral prefrontal cortex (Heinze et al., [2014](#)).

Findings such as these have led some researchers to hypothesize that each hemisphere plays somewhat of a complementary role in planning and sequencing. The left hemisphere may be more involved in creating subgoals, while the right hemisphere is more involved in considering the relationships between those subgoals (Kaller et al., [2011](#)). Consider, for example, the goal of making pasta for your dinner guests who are arriving in 45 minutes. From this viewpoint, the left hemisphere would be more involved in setting the subgoals: assembling and combining the correct ingredients for the sauce, starting the boiling water for the pasta, getting the requisite sauce pan and utensils on the stove, and the logical ordering of those subgoals. For example, you can't start combining the ingredients before you've gotten the sauce pan and utensils on the stove.

The right hemisphere in a complementary manner considers what intermediate moves may be needed that don't directly address those subgoals but are required, as well the interrelationship between those goals. For example, while the subgoal may be to get the requisite sauce pan and utensils on the stove, if they are dirty, you will need to postpone that goal and wash the items first. And while washing them either by hand or in the dishwasher will serve that purpose, if the goal is to have dinner ready by the time of your guests' arrival in 45 minutes, then washing the saucepan by hand is the better option.

In fact, when Tower of London problems were designed so that they placed more of a demand on the former abilities – the logical sequencing of the subgoals – there was greater activation over left DLPFC than right DLPFC. In contrast, when the subgoals required intermediate steps that did not place a ball in its final position, there was more right DLPFC activity than left DLPFC activity (Kaller et al., [2011](#)). Suggesting that the interrelationship between these regions is important for task performance, the characteristics of interhemispheric white matter that connect these regions predicts how well people perform on the task (Kaller et al., [2015](#)).

Rostrolateral prefrontal cortex (BA 10) may also become involved in solving problems on the Tower of London as the number of moves required to reach a solution increases (Wagner et al., [2006](#)). These findings are consistent with the work we described in the [previous section](#) suggesting that this region is important for selecting overall goals or subgoals.

Neuroimaging research with another paradigm provides converging evidence. In this paradigm individuals had to complete simple predesignated sequences of tasks (e.g., a sequence of four decisions about items: color, color, shape, shape). Activity in rostralateral cortex (sometimes referred to as lateral regions of orbitofrontal cortex) increased with sequence position. Moreover, the degree of activation in this region “resets” at the beginning of each new sequence. Additionally, TMS over the rostralateral prefrontal region, but not a more medial anterior region nor over premotor regions, increasingly disrupts performance with increasing position in the sequence (Desrochers et al., [2015](#)). Such findings are consistent with the idea that rostralateral prefrontal cortex is involved in higher-order processing of sequences to reach a goal.

In sum, dorsolateral prefrontal cortex and frontopolar cortex appear to play an important role in sequencing and planning behaviors. DLPFC may play a specific role because planning requires that information in working memory is continually re-ordered and updated. Frontopolar regions may be involved because they are responsible for integrating multiple subgoals.

Shifting Set and Modifying Strategies

So far we have presumed that attaining a goal simply requires determining what steps to take and then performing them. However, as we all know, the path to a goal is not always a simple linear progression; we often encounter some unexpected twists and turns. For example, when cooking sauce for making pasta, the phone may ring. At this point, a task-switch is necessary. One must now go and answer the phone because it may be your friends whom you have invited over to dinner calling to ask about what wine to bring or to say that they are going to be late. However, you cannot let that conversation go on for too long, as you will need to switch back to your original task of cooking lest your sauce burn and your dinner be ruined! As we discussed earlier, at least some models assume that task-switching is a fundamental underlying process that supports executive function.

The classic neuropsychological test used to examine task-switching is the [Wisconsin Card Sorting Test \(WCST\)](#). In this test, four cards are laid on the table in front of the participant. Each card is distinct from all the others on the basis of three attributes: the number of items on the card (one, two, three, or four), the shape of the items on the card (circle, triangle, cross, or star), and the color of the items on the card (red, green, yellow, or blue). For example, one card might have three yellow crosses and another two green stars. The person is then given a stack of cards and is told to sort them into four piles below the four cards already on the table. However, no explicit criteria for sorting are given. Rather, as the individual places each card onto one of the four piles, the experimenter indicates only whether the response is correct or incorrect. From the experimenter's feedback, the person must deduce the dimension on which the card should be sorted (e.g., color). An example of this procedure is shown in [Figure 11.9](#).

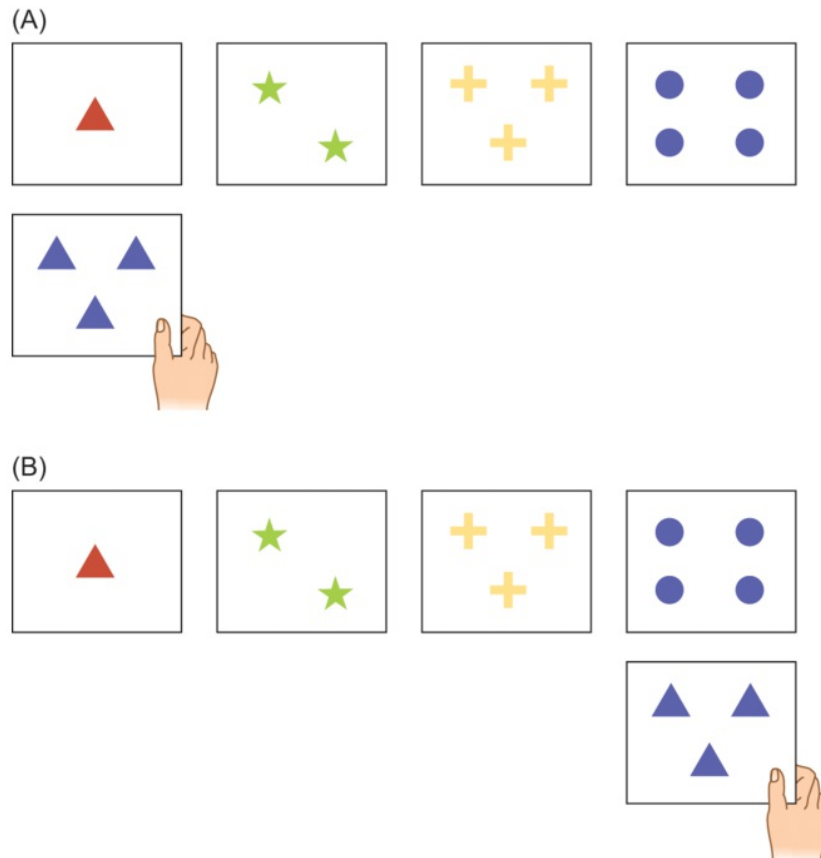


Figure 11.9 Two examples of sorting behavior on the Wisconsin Card Sorting Test.

For this particular series of trials, the individual must sort the cards on the basis of their color. (A) An example of an incorrect sort; the individual matched the card on the basis of shape instead. (B) An example of a correct sort; the individual matched the card on the basis of color rather than shape or number.

After the participant correctly sorts 10 cards on the basis of one particular attribute, such as color, the experimenter, without explicitly telling the participant, changes the criterion for sorting the cards (e.g., to shape). Neurologically intact people quickly realize that although their behavior previously led to a correct response, it no longer does so. Thus, they adjust their responses accordingly. In contrast, people with executive dysfunction perseverate, which is the action of continuing to engage in the same behavior. In this case, they sort the cards by the same attribute despite receiving negative feedback about their choice. The lack of control of action exhibited by these patients can occur even when the person appears to “know” how to act. Patients with

executive dysfunction will persist in sorting on the basis of a previously correct but now incorrect category even as they state that they know their action is wrong (e.g., Milner, [1963](#)).

Classically, this test was considered very sensitive to frontal lobe damage, although people with damage to other regions of the brain may also perform poorly on the task (Nyhus and Barceló, [2009](#)). A review of studies using this task finds that patients with frontal lobe damage tend to do worse than those with posterior damage, and those with damage to the dorsolateral prefrontal area tend to perform the poorest (Demakis, [2003](#)).

Many neuroimaging studies have found activation of DLPFC along with ventrolateral prefrontal cortex during performance of the WCST. In addition, activity in the inferior parietal lobe, temporoparietal association cortex, and the basal ganglia is often observed (Nyhus and Barceló, [2009](#)). This diversity of brain regions activated by the task highlights the fact that the WCST is a complex, multifaceted task, as are many tasks originally designed with the intent of detecting brain damage. The person must be able to switch categories, but also to create a rule that will guide sorting, to keep in mind (in working memory) the outcomes of prior trials, and to use deductive reasoning. We discuss these other processes, such as rule generation and deduction, in a later section of this chapter. Here we focus on set-shifting.

One of the main components of the WCST is task- or set-switching. Evidence from neurologically intact people suggests that switching between two tasks is not easy for anyone. It is easier to keep doing what you are doing than to switch from one task to another. Moreover, task-switching is likely to be directed by an executive control system that is independent of the systems that actually perform each task (Monsell, [2003](#)).

Psychological research has shown that there is a cost to switching between tasks, which is difficult if not impossible to eliminate. In a typical task-switching study, individuals are asked to view a stimulus, such as a colored letter. Prior to the trial, a cue indicates the attribute that should be used to make a decision. For example, the participant may have to indicate whether the letter is printed in green or red, or whether

the letter is a vowel or a consonant. On some trials, which are referred to as repeat trials, the person performs the same task as on the prior trial (e.g., “determine color” followed by “determine color”). On other trials, which are referred to as switch trials, the person performs a different task than on the prior trial (e.g., “determine color” followed by “determine consonant/vowel”).

Typically, response times are longer for switch trials than for repeat trials, known as the **switch cost**. This increase in response-time length reflects two factors: a need to inhibit or overcome the prior task set, sometimes referred to as task-set inertia, and the need to configure the system for the current task set. A typical manipulation in such studies is to vary the time between when the cue is given and the stimulus appears. Increasing the cue–stimulus interval reduces the switch cost, most likely because the person has additional time to configure the new task set before that task set must be used on the stimulus. Typically, however, even with long delays, it is impossible to completely erase or eliminate the switch cost, presumably reflecting task-set inertia. Intriguing recent evidence from ERPs provides some measure on switch trials of how much activation remains from a prior task set. The larger the ERP signal associated with the prior task on switch trials, the larger the behavioral switch cost, providing evidence that task-set inertia contributes to switch costs (Evans et al., [2015](#)).

Patients with left frontal lobe damage have a specific deficit in task-switching, especially when there are no strong or obvious cues as to which task should be performed when (Rogers et al., [1998](#)). Moreover, they have difficulty regardless of whether the switch involves a conceptual set (e.g., switching from sorting animals by where they live to sorting by their degree of ferocity) or a perceptual set (e.g., switching from sorting based on color to sorting based on shape) (Delis et al., [1992](#)). The nature of this difficulty may be compounded by other factors, depending on the side of the lesion. In patients with right inferior frontal lobe damage, an inability to exert inhibitory control (which we discuss in one of the following sections) may make task-switching even more difficult, whereas an inability to maintain a task set may exacerbate difficulty

in task-switching in patients with damage to left dorsolateral prefrontal regions (Aron, Monsell et al., [2004](#)). Conversely, increasing activity over the (left) dorsolateral prefrontal cortex via transcranial direct current stimulation can augment task-switching abilities (Leite et al., [2013](#); Tayeb and Lavidor, [2016](#)).

The important role of prefrontal regions in task-switching is corroborated by brain imaging studies. Meta-analyses across studies indicate that the inferior frontal junction, which resides at the base of dorsolateral prefrontal cortex and inferior frontal cortex (see [Figure 11.10](#)) plays a prominent role (Derrfuss et al., [2005](#)), reducing interference between items in task-switching. Nonetheless, a number of neuroimaging studies, as well as studies with brain-damaged patients, suggest that there is not one particular region of the brain that metaphorically flicks the switch from task A to task B. Rather, this region appears to activate along with the posterior parietal lobe and other portions of the frontoparietal network during most task-switches in a domain-general manner, that is, regardless of the particular tasks being performed (Wager et al., [2005](#); Kim et al., [2012](#)). Corroborating evidence comes from monkeys who, when doing a task-switch, show synchronous activity over prefrontal and parietal regions in the 5–10 Hz range (Phillips et al., [2014](#)).



Figure 11.10 (A) The location of the inferior frontal junction that has been shown to play a prominent role in switching between two tasks. (B) The green line depicts the position of the slice shown in (A).

In addition to activation of brain regions involved in switching in general, activation is also observed in additional brain regions. These regions vary depending on the type of switch (e.g., based on perceptual or abstract information) (Kim et al., [2012](#)), and depending on the degree of similarity or dissimilarity between the task sets (Wager et al., [2005](#)). In sum, these findings suggest both a somewhat general mechanism that helps to facilitate the switch between tasks as well as the involvement of more specific brain regions depending on the nature of the actual tasks themselves (e.g., a task involving decisions about color versus a task involving decisions about form).

To illuminate the idea of task-set similarity, look at the task illustrated in [Figure 11.11](#), which was originally designed for use with animals. Participants are first taught to discriminate between two items (e.g., two black shapes) and to respond to only one of them. Then another dimension is added to the items (e.g., a simple white line pattern), which is to be ignored ([Figure 11.11A](#)). At this point, new stimuli consisting of novel shapes and novel white line patterns are introduced. In one condition, the intradimensional shift condition, the discrimination is to be made solely on the basis of the same dimension used previously (e.g., on the basis of the black shapes, while ignoring the white line pattern) ([Figure 11.11B](#)). In the other, the extradimensional shift condition, the participants must respond to the dimension that was previously ignored (e.g., the white line patterns) ([Figure 11.11C](#)).

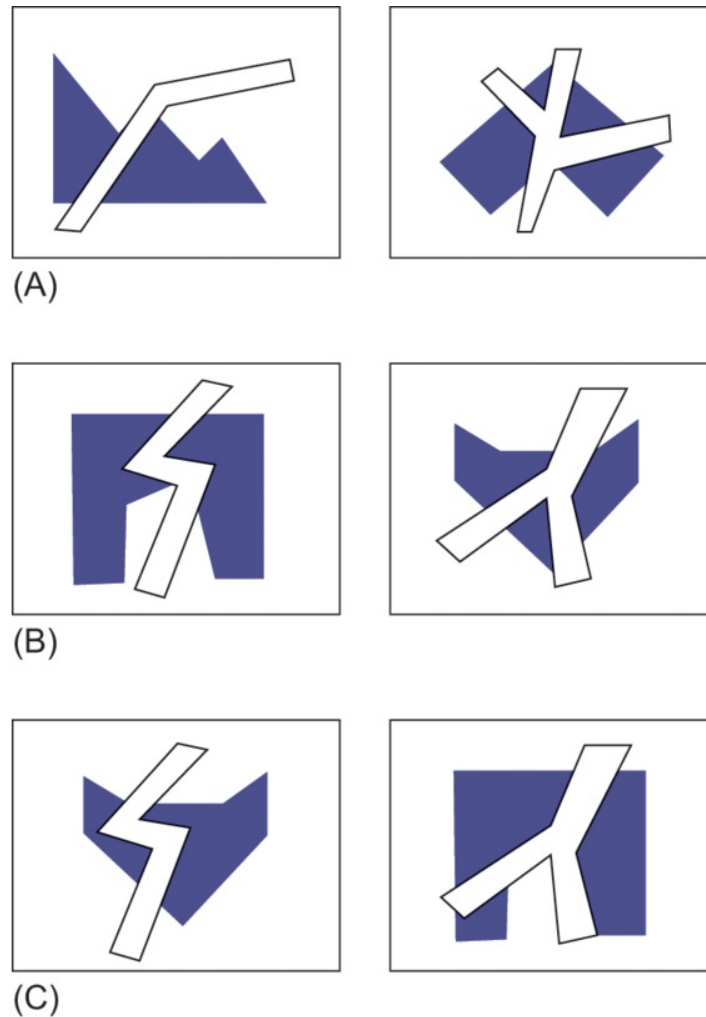


Figure 11.11 Intradimensional versus extradimensional shifts.

(A) Participants are first taught to respond to one of two black shapes and to ignore the white shapes on top of them. (B) In an intradimensional shift, people must learn to discriminate between two new black shapes while continuing to ignore the white shapes. (C) In an extradimensional shift, people must now discriminate between the two white shapes, which is the feature that was previously ignored. Patients with frontal lobe damage have difficulty with this extradimensional shift.

Compared with patients who have temporal lobe lesions and with neurologically intact individuals, patients with frontal lobe damage are deficient at the extradimensional shift but not at the intradimensional shift (Owen et al., [1991](#)). Both PET and fMRI studies suggest greater activity in prefrontal cortex, including left anterior polar frontal cortex and right DLPFC, for extradimensional as compared to

intradimensional shifts (Rogers et al., [2000](#); Nagahama et al., [2001](#)). Thought of differently, if a new strategy is similar enough to the old one, the frontal lobe is not required. But if a shift to a new set is needed, having a functional frontal lobe helps!

The frontal cortex may be especially involved in set-shifting when the shift must occur between relatively abstract task sets. For example, studies find that damage to frontal regions only interferes with task-switching when the rules are abstract (e.g., decide if the letter is a vowel or a consonant; decide if the number's value is greater than five or lower than five) but not perceptually based rules (e.g., name the letter, name the number) (Kehagia et al., [2014](#)). Similarly, neuroimaging studies indicate greater activation of the frontal cortex when one must shift between sets of abstract rules, whereas the parietal lobe may play a more important role when one must shift between sets of perceptual features (Ravizza and Carter, [2008](#)). And finally, when switching between tasks with complex multifaceted rules, TMS over frontopolar regions increases switch costs, an effect that is not observed for simpler rules (Bahlmann et al., [2015](#)).

Further complicating the picture are findings that the brain regions involved in task- or set-shifting vary depending on what aspect of the switching is most important. For example, dorsolateral prefrontal regions may be more involved in task-switching by tackling the interference in working memory from the prior task set, whereas the anterior cingulate cortex may be more involved in reconfiguring response priorities for the task, such as which responses should be utilized under which conditions (Hyafil et al., [2009](#)). And different regions may be involved in overcoming the inertia from a prior task set as compared to reconfiguring for a new task set (Witt and Stevens, [2012](#); Whitmer and Banich, [2012](#)).

If at this point you feel like most of the brain is involved in task-switching, you may not be far off. Our short review here makes an important point: task-switching is likely subserved and enabled by a large network of brain regions, with certain components playing a more prominent role than others, depending on the situation. The idea that this ability is supported by a network is reinforced by findings that task-switching also depends on factors that affect connectivity between brain regions. For example, reduced

white matter in the elderly is associated with poor performance in task-switching (Gratton et al., [2009](#)). In addition, individuals who show smaller switch costs (i.e., more efficient switching) have great connectivity, at rest, of the inferior frontal junction with parietal regions (Yin et al., [2015](#)). Thus, connectivity between regions, especially the frontal and parietal, may play as important a role as the regions themselves in supporting set-shifting.

Self-Monitoring and Evaluation

Another skill that is important for attaining a goal is the ability to evaluate whether your performance is actually bringing you closer to your goal. Stated more simply, it is the ability to accurately answer the question, “How am I doing?” People with executive dysfunction have difficulty evaluating or monitoring their performance. For example, given cards that must be rearranged in a sequence, people with executive dysfunction may simply move a card or two and then declare themselves done. Lack of motivation or concern about their performance level accounts for some of these difficulties, especially considering the changes in emotional processing that accompany frontal lobe damage (which we discuss in [Chapter 12](#)). Lack of motivation, however, is unlikely to be the sole explanation for these difficulties because in some situations, patients verbally declare that they should do something but then fail to follow through. The verbal declarations provide some evidence that the person is actually engaged by the task and has a degree of interest in reaching the goal. However, the ability to monitor performance or to specifically translate that idea into action is disrupted.

Not surprisingly, the ability to evaluate one’s own behavior is affected by frontal lobe lesions, like all the other abilities described in this chapter. First, metacognitive awareness, that is, an overall evaluation of one’s performance, is disrupted in patients with left or right frontal lesions. On questionnaires about their behavior, such patients are likely to say that they are organized or don’t drift off task, when those close to them, such as family members and caregivers, disagree. This deficit does not arise from brain

damage in general, as patients with lesions to left or right posterior regions are significantly more realistic in their self-assessment (Hoerold et al., [2013](#)).

In addition, frontal damage, especially right frontal damage, impairs the ability to detect errors during a sustained attention task and to modify ongoing behaviors to take a corrective action. For example, when participants have to move their arm to touch a target location and the target unpredictably “jumps” to a new location after initiation of movement, patients with right frontal damage show a significant delay in the corrective movement (compared to left frontal patients) (Mutha et al., [2014](#)).

This latter issue of how people monitor their performance and detect when they have erred has received much investigation. The results of this body of research indicate that we have a particular set of brain mechanisms that helps to monitor our performance and detect errors (see Gehring et al., [2012](#), for review). Evidence for one such mechanism comes from an ERP signal known as the [error-related negativity \(ERN\)](#). This component, which was discovered about two decades ago, occurs approximately 100 ms after an error has been made (Falkenstein et al., [1991](#); Gehring et al., [1993](#)) ([Figure 11.12](#)). The ERN has been specifically linked to error monitoring because its amplitude increases under conditions in which response accuracy is emphasized versus speed, and because the larger the error (pushing the button with the wrong hand as well as the wrong finger), the larger the amplitude of the ERN. When scientists are talking about this component and being less scientifically precise, they refer to it as the “blunder blip.”

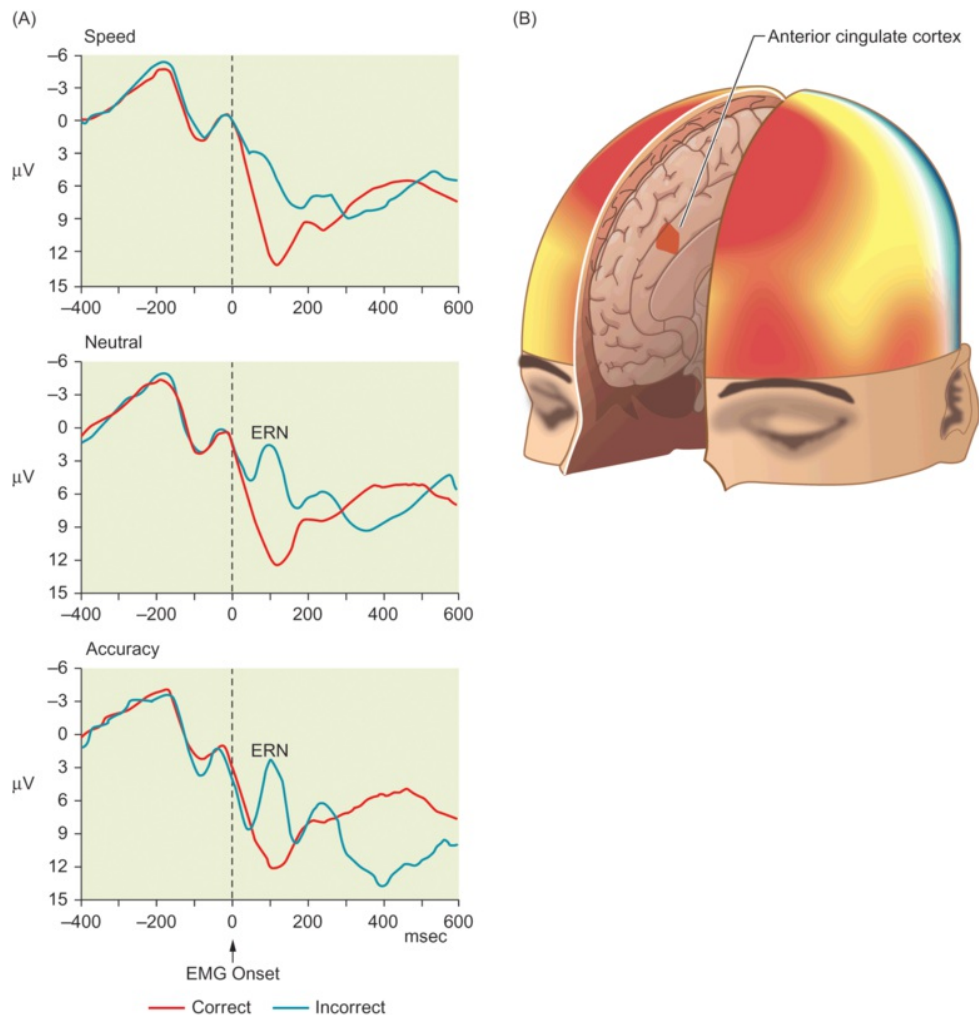


Figure 11.12 The error-related negativity (ERN).

(A) The effect of emphasizing speed versus accuracy on the ERN. In these graphs, negative electrical potentials are plotted on the upper portions of the graphs and positive potentials on the lower portions. Notice that the response to errors (shown in blue) peaks about 100 milliseconds after the beginning of the muscles' movement (as denoted by EMG onset). Also notice that the size of the ERN is much greater when accuracy is stressed (bottom panel) rather than speed (top panel). (B) The area of the anterior cingulate that is thought to generate the ERN.

(from Taylor et al., [2007](#))

A variety of converging evidence suggests that the ERN component arises from rostral regions of the anterior cingulate, located on the medial portion of the frontal lobe. This evidence includes research using dipole modeling of ERPs (Dehaene et al.,

[1994](#)), activation as assessed by fMRI (Kiehl, Liddle et al., [2000](#)), simultaneously recorded EEG and fMRI (Debener et al., [2005](#)), studies using MEG (Keil et al., [2010](#)), and the results of a unique patient from whom intracranial recordings were made from the anterior cingulate (Pourtois et al., [2010](#)). Consistent with this idea, individuals with damage to medial prefrontal regions are slow to correct erroneous responses (e.g., Hochman et al., [2015](#)).

The exact role of medial prefrontal regions with regard to self-monitoring and evaluation remains a matter of debate. One initial suggestion was that the anterior cingulate actually detects that an error has been made (e.g., Scheffers et al., [1996](#)). But other evidence suggests that even when a person is not aware of an error, an ERN can be still be detected (Nieuwenhuis et al., [2001](#)), as can medial prefrontal activity in the region thought to produce the ERN (Hester et al., [2005](#)). Hence, it may be that the ERN is just providing a rather undifferentiated signal that something is amiss (Kieffaber et al., [2016](#)).

Instead, awareness of an error seems to be indexed by another component, the **[error positivity \(Pe\)](#)** (e.g., Davies et al., [2001](#)), which frequently follows the ERN by about 200–300 ms (see [Figure 11.13](#)). At present, the neural source of this latter component remains unclear, with some work suggesting that it is generated in the posterior insula (Dhar et al., [2011](#)) and others suggesting it is generated in the anterior insula (Ullsperger et al., [2010](#)). The insula is a brain region that is associated with **[interoception](#)**, the ability to sense the physiological condition of the body (Craig, [2011](#)). Localization of the error positivity to this region of the brain seems reasonable, as we have all experienced that “Oops” feeling in the pit of our stomach, or perhaps a bit of heart racing as well, when we realize that we’ve made a big mistake.

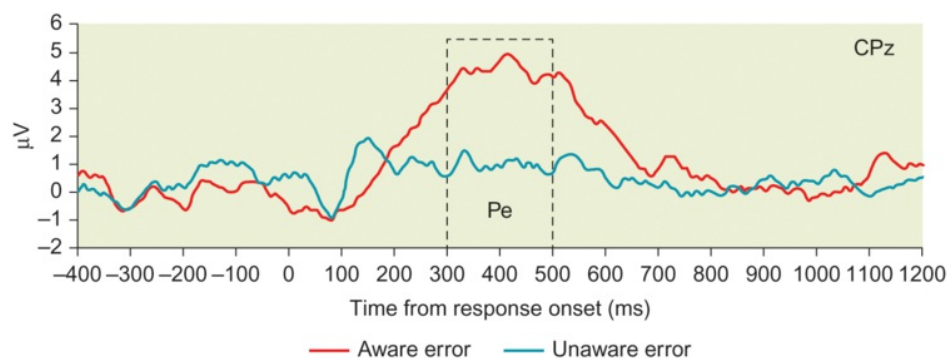


Figure 11.13 The error-related positivity.

This ERP component is observed between 300 and 500 milliseconds after a response is made and is larger when a person is aware of an error compared to when she or he is not. It is usually best detected over electrode CPz (refer back to Chapter 2, page [49](#)), consistent with it being generated in the insula.

(from Hoonakker et al., [2016](#))

The exact computation that the medial prefrontal regions perform to detect and correct errors is a source of lively debate in the field right now. Here we provide just a brief overview of some of the ideas that scientists are currently considering. One viewpoint is that medial prefrontal cortex does not so much detect errors as it monitors for conflict. It becomes active during error detection because errors usually occur when there is conflicting information (e.g., Carter et al., [1998](#); Botvinick et al., [2001](#), [2004](#)). It is posited that when the cingulate detects conflict, it sends a signal to dorsolateral prefrontal cortex to ramp up the top-down control it is exerting, so as to reduce conflict, and hence errors, in subsequent behavior.

Other theories (Walton et al., [2003](#); Shenhav et al., [2013](#)) argue that the medial prefrontal cortex determines whether exerting control is worth the effort and cost in a given situation. For example, consider a situation in which you are determining how closely you are going to monitor what you are about to say. Evaluating and crafting everything you are about to say before the words come out of your mouth is quite effortful. If you are at a party with friends, you are likely to decide that such effort is not worth it. If you make an “error” and say something rash, your friends are likely to

forgive you because they know you're a good person. And it's hard to be spontaneous with your words if you are internally continually editing them. On the other hand, if you are in an important job interview, such effort might well be worthwhile to make a good impression as a thoughtful and informed person and to avoid saying something that would keep you from getting the job. This idea is consistent with ideas we discussed earlier in the chapter suggesting that the anterior cingulate is important for the initiation of behavior and exerting effort.

Other models suggest that the cingulate is focused on determining whether the action you just took leads to a useful or good outcome. Some versions of this viewpoint argue that medial prefrontal cortex is particularly sensitive to negative outcomes or the loss of rewards, while others argue that it calculates the differences between the expected outcome of an action and the actual outcome regardless of whether that outcome is positive or negative (Alexander and Brown, [2011](#)). In this way, the history of the outcomes of an individual's recent behaviors can be used to guide subsequent actions and responses so as to avoid future "errors" (Holroyd and Coles, [2002](#), [2008](#)). Consistent with this idea, the ERP is also elicited by monetary loss (Gehring and Willoughby, [2002](#)) or the unexpected lack of a reward (Holroyd et al., [2003](#)). From this viewpoint, the ERN may, in part, reflect the subjective evaluation of performance ("Oh damn, I think I just messed up and didn't get what I wanted"), rather than whether one did indeed make an error. Support for such a viewpoint comes from findings that the amplitude of the ERN is influenced by mood, such as high levels of subjective distress (Luu et al., [2000](#)); is amplified in individuals who have obsessive-compulsive disorder (Fitzgerald et al., [2005](#)); and is larger when a person makes an error that leads to a monetary loss as compared to a monetary gain (Taylor et al., [2006](#)).

Empirical work suggests that different regions of the cingulate may be involved in the prediction of the outcome of an action as compared to the evaluation of the outcome. More specifically, the prediction is thought to be generated by pregenual and posterior

regions of the anterior cingulate, with the evaluation of outcome performed by the region in-between, the mid-dorsal ACC that extends into SMA (Jahn et al., [2014](#)).

Before we leave this topic, it is worth noting that the activity of error monitoring and evaluation systems in the brain is influenced by differences amongst people (van Noordt and Segalowitz, [2012](#)). For example, people who are anxious tend to show an increased ERN (Proudfit et al., [2013](#)), with the relationships stronger for those who show a high level of worry (Moser et al., [2013](#)). In contrast, those who may not be as adept at monitoring and evaluating decisions, such as people with substance use disorder (e.g., Franken et al., [2007](#)) or those with attention-deficit/hyperactivity disorder (Shiels and Hawk, [2010](#)) show decreases in the ERN and Pe. We discuss this issue in more detail in [Chapter 14](#).

Finally, as we have emphasized at many points in this chapter, there is unlikely to be a one-to-one mapping between a particular piece of frontal cortex and a specific function such self-evaluation. This point is reinforced by data from patients with circumscribed lesions to specific regions of the frontal lobe. At least some abilities relating to evaluation and monitoring are intact in patients with damage to the anterior cingulate cortex, indicating that the anterior cingulate is not the sole “error detector” of the brain. Patients with cingulate damage are able to report errors. Moreover, they exhibit a behavior typically observed after errors, known as [post-error slowing](#), which is the phenomenon that people respond more slowly on the next trial after an error. However, although patients with cingulate damage can correct their errors, they do so very slowly, suggesting a deficiency in on-line aspects of error detection.

Conversely, damage to other brain regions, including lateral prefrontal cortex, can compromise monitoring and evaluation. Often, in reaction-time tasks when people know they’ve made an error, they go on and press another button, a self-corrective action. Furthermore, the force with which a response is made is usually less on error trials, as if the system were detecting conflict and “holding back” a bit. Patients with damage to lateral PFC exhibit neither of these traits when making errors. Moreover, these

individuals show as large an ERN to correct trials as they do to incorrect trials (e.g., Gehring and Knight, [2000](#)). And still other evidence from brain-damaged patients suggests that error evaluation can be altered by damage to the basal ganglia (Hochman et al., [2015](#)).

Thus, these findings suggest that there is not a single region of the brain that is important for the monitoring of action and detection of errors, but rather that this system is likely to involve a number of regions, including the anterior cingulate cortex, lateral prefrontal regions, and the insula, as well as their interaction (e.g., Neta et al., [2016](#)). In fact, evidence from EEG recordings suggests that there is a cascade of activity that occurs across a variety of brain regions that unfolds over time as we make choices and act upon the world. These brain regions detect and weight the accumulating evidence that provides evaluation of our actions and uses that to determine the subsequent actions or reactions that are likely to be required (Ullsperger et al., [2014](#)).

Inhibition

One last, critical aspect of goal-directed behavior is the ability to override or interrupt processing. The inability to stop, interrupt, or abort inappropriate responses, often referred to as inhibition or [response inhibition](#), is considered by some models to be a major subcomponent of executive function. As we have discussed, perseveration is one of the hallmarks of executive dysfunction, and it is easy to see how a disruption in inhibitory control could lead to such behaviors. If one cannot override inappropriate responses, perseveration will result. In fact, patients with frontal lobe damage perform poorly on tasks that require inhibitory control (Knutson et al., [2015](#)). This is especially true when well-linked associations must be overridden. For example, if patients with frontal damage have learned to consistently make a motoric action in response to a particular visual symbol, they have much difficulty inhibiting that response when another cue (e.g., a sound) indicates that they should withhold that response (e.g., Rieger et al., [2003](#)).

Response inhibition has been investigated in neurologically intact people using a number of paradigms. One commonly used task is the [Go/No-Go task](#). In this task, the person responds by pushing a button when certain visual stimuli appear (Go trials) and withholds response to other stimuli (No-Go trials). Response inhibition is quite difficult if the No-Go trials are relatively rare. When Go responses are expected in this manner, they are said to be prepotent, meaning that the system is biased to produce them. Withholding a response has consistently been found to engage a right-sided network of regions, including the right middle and inferior frontal cortex, the pre-SMA, and parietal cortex.

Another task used to examine the inhibition of responses is the stop-signal task. In this task, the person must respond as quickly as possible to a stimulus that appears on the screen. However, on a minority of trials, very shortly (e.g., one-quarter of a second) after the stimulus is presented, another signal (e.g., auditory tone) occurs indicating that the response should be aborted. This task is somewhat different from the Go/No-Go task: rather than overriding the tendency to produce a prepotent response, here the person must actually cancel an ongoing response. This task too activates a large network of brain regions, very similar to that observed for the Go/No-Go task. Both tasks activate a wide range of brain regions spanning (dorso)lateral prefrontal cortex, the anterior cingulate, SMA, pre-SMA, insula, and parietal regions (Swick et al., [2011](#)).

Which of these various regions are essential for inhibition, and which aspects of inhibition they support are not clear. Some scientists have suggested that certain portions of this network, such as right inferior frontal cortex, may be specifically involved in response selection and override. Supporting the conclusion that the right inferior frontal region is critical for response inhibition, damage to this region impairs performance on the stop-signal task, and, moreover, the degree of damage predicts performance (Aron et al., [2003](#)). Currently there is a debate as to whether medial prefrontal regions, such as the SMA, pre-SMA, and anterior cingulate also aid in the stopping of actions (Roberts and Husain, [2015](#); Li et al., [2006](#); Sharp et al., [2010](#)).

Some work suggests that different neural pathways from the right inferior frontal cortex may be involved in different types of stopping. In both cases, the inhibition of motor acts is thought to occur via connections between the right inferior frontal cortex to the subthalamic nucleus, which is part of the indirect pathway of the basal ganglia. As you may remember from Chapter 4 (see page [109](#) and [Figure 4.9](#)), the indirect pathway is thought to be important for suppressing unwanted movement. It has been suggested that when you want to stop one response in favor of another, the right inferior frontal cortex sends a signal to the subthalamic nucleus via the striatum, the starting point of the indirect pathway. However, if your goal is to stop all motor activity, either totally or just for a short period of time (such as in a pause of activity), the signal is sent from the right inferior prefrontal to the subthalamic nucleus via a hyperdirect route (Aron, Robbins, and Poldrack, [2004](#), [2014](#)).

However, other research has called into question the idea that the right inferior prefrontal region is specifically involved in inhibiting responses, suggesting rather that it plays a more general role in altering responses. Some of the strongest evidence for this viewpoint comes from a study in which neural activation was recorded under two conditions. One condition was a standard Stop-Signal condition in which the signal indicated that the response should be aborted. In the other condition, the signal indicated that an additional response should be made (i.e., a Double-Go) condition. If the right inferior frontal cortex is specifically involved in inhibiting responses then activation should only be observed in the former condition but not the latter. However, the researchers found identical degrees of activation in right inferior prefrontal regions for both the Stop and Double-Go conditions suggesting a more general role of this region in altering responses (Hampshire et al., [2010](#); Chatham et al., [2012](#)). According to these researchers (Chatham et al., [2012](#)), right inferior frontal regions are involved in monitoring the current environmental context so as to provide information about how goals can be met. In this paradigm, the right inferior frontal cortex may monitor the external environment for signals that indicate that goals should be halted (as on No-Go trials) or modified (as on Double-Go trials). As you may remember from Chapter 10

(see page [317](#)), right inferior frontal regions and the anterior insula are associated with the ventral attention network that monitors for salient environmental events. Consistent with such an idea, activity is consistently observed in the stop-signal task in regions of the anterior insula bilaterally and the thalamus (Swick et al., [2011](#)). While the exact role of inferior frontal regions versus the insula is not clear, at least some research suggests that the insula may be more involved in monitoring for salient events, while the right inferior frontal cortex then uses that information to help exert the necessary cognitive control that will lead to desired outcomes (Cai et al., [2014](#)).

Also to be determined is the exact role that the lateral prefrontal cortex plays in inhibitory control. Dorsolateral prefrontal cortex also shows more activation on Go than No-Go trials. Data from patient studies (Krämer et al., [2013](#)) and meta-analyses (Criaud and Boulinguez, [2013](#)) indicate that in many cases when stopping is required there are increased demands on cognitive control and working memory, activities supported by lateral prefrontal cortex. For example, activity on No-Go trials may require more control not because they are associated with a cessation of action per se, but rather because they are associated with an atypical action in the face of a more prepotent response (i.e., pressing a button on Go trials) (Nee et al., [2007](#)).

From this perspective, response inhibition may be a more specific example of a more general function, that of [interference resolution](#), which is the ability to resolve conflict between competing information or distracting information that might interfere with performing a task. A nonmotoric example of a task requiring interference resolution is the Stroop task, in which, on incongruent trials (e.g., the word “red” in blue ink), one must resolve the interference between the ink color of the item itself and the color named by the word. Both motoric and nonmotoric tasks that require interference resolution activate the dorsolateral prefrontal cortex, anterior cingulate cortex, inferior frontal regions, and posterior parietal cortex (Nee et al., [2007](#)), all part of the executive control network. When participants have to engage across three distinct types of inhibitory tasks – one which requires stopping of a motor response, one that requires stopping of memory retrieval, and the third that requires the stopping of an emotional

reaction – overlapping regions of the dorsolateral prefrontal cortex become active (Depue et al., [2015](#)). These findings suggest a general mechanism for cognitive control over inhibitory processes and not one that is specific to motoric inhibition.

Recently researchers have taken this idea even a step further. To determine the factors underlying executive function, one can look at the correlation in performance across individuals on a wide variety of executive function tasks. Studies examining performance across individuals on a broad range of executive function tasks do not find that inhibitory control tasks show a specific correlation among one another, which would be expected if inhibition is an isolatable aspect of control. Rather, inhibitory tasks load highly on the common executive function factor we discussed earlier (Miyake and Friedman, [2012](#)). As you may remember, this factor is thought to reflect the ability to actively maintain a goal in working memory, especially in the face of distracting information or when maintaining that information is difficult. Inhibitory tasks may not tap “inhibition” per se, and response inhibition may not be a separable executive process per se (for the details of this argument see Munakata et al., [2011](#)). Rather, inhibitory tasks may make it particularly challenging to maintain a goal because a prepotent response or action must be overridden.

Whereas this debate as to whether there is really such a concept such as inhibition or not may seem like an abstract semantic argument, it has important implications for the real world. For instance, consider the example of teaching a child to refrain from or inhibit an unwanted behavior. What would be the best way to do so? If there is a special inhibitory module in the brain, it might be best to train it to teach children to “Just say no.” On the other hand, if tasks that require inhibition are really very taxing on maintaining a goal, then it would be more effective to teach children to keep a goal in mind (i.e., “Keep your eye on the prize”). In fact, research suggests that training children to keep goals in mind is actually more effective than teaching them to stop their behavior when you wish them to inhibit a response (Chevalier et al., [2014](#)).

One way to integrate all of these findings is to suggest that inhibition may occur in different ways and through different neural circuits. For example, in some cases, you can indeed inhibit unwanted behaviors, thoughts, and actions by keeping your eye on the prize, that is, keeping your goal front and center. The DLPFC may play a prominent role in doing so. Another way to inhibit unwanted or undesirable behaviors may indeed be to monitor your environment for changing conditions so that you are aware of which behaviors are most desirable or possible in the current context, and which would be counterproductive and undesirable. The right inferior frontal cortex, as part of the attentional network involved in processing salient environmental stimuli and events (see Chapter 10, page [317](#)), may help to enable such decisions. When the conditions merit a need to change your behavior, interactions of the right inferior frontal cortex with the basal ganglia's indirect pathway may help you to inhibit the current response and replace it with another.

And finally, when it is necessary to quickly and immediately stop all ongoing behavior, the hyperdirect pathway from the right inferior frontal cortex connection to the subthalamic nucleus may allow you to cease all motor action. This cessation mechanism may inhibit that motor action indefinitely, such as when you are at a party and stop yourself in mid-reach from grabbing that delicious-looking cookie on the table and walk away never to return. Or alternatively this hyperdirect pathway may enable you to cease and pause your behavior just long enough to evaluate the situation a bit more after which you determine that since they are not serving any alcohol, you can “spend” your calories on the cookie and now allow yourself to grab it. (See Wessel and Aron, [2017](#), for further discussions of conditions that engage interactions between the right inferior frontal cortex and the basal ganglia so as to inhibit motor behaviors.)

In Focus: Can You Inhibit a Memory?

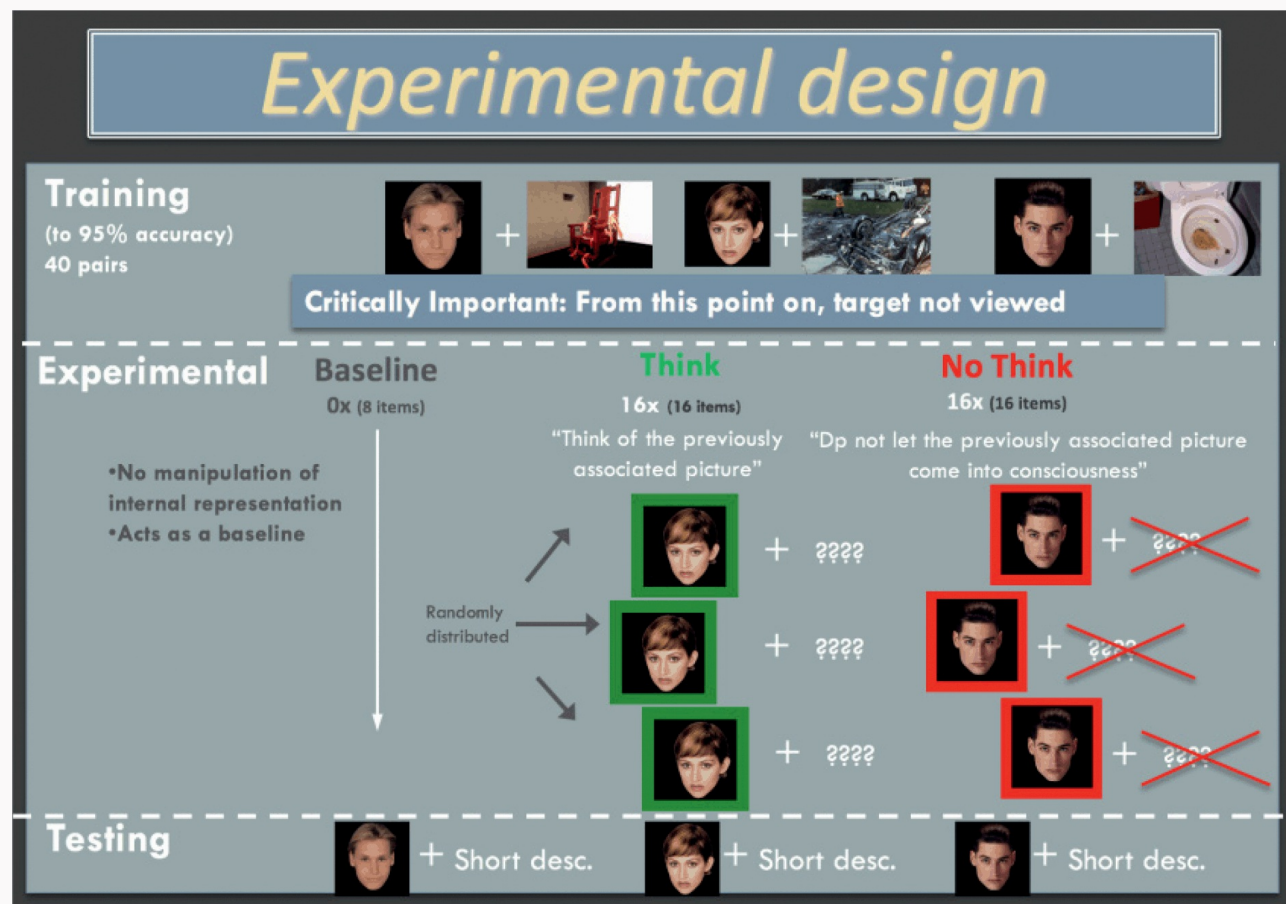
In this section we have been talking about inhibition mainly from the perspective of inhibiting or suppressing a response. However, within the field of psychology

there is a long history, going back to Freud, of considering whether memories and thoughts can be inhibited. Freud proposed that one mechanism by which we protect ourselves from unwanted thoughts or desires is to repress them. He viewed this repression as an unconscious process rather than one that is effortfully controlled, but central to his idea is that an individual is able to control access to a memory, and, in effect, to inhibit or suppress it. This idea has been very controversial; in fact, it has been referred to as “a clinical myth in search of a scientific explanation.” Moreover, the issue of whether memories that have supposedly been repressed can then be brought back into consciousness has been hotly debated; there is strong contention about whether “repressed” memories actually exist or whether they are in fact false and/or induced memories.

As you might imagine, investigation of whether such an inhibitory process exists is quite difficult. However, to determine in principle whether a memory could be inhibited, one would need two conditions to be met. First, one would need to know that the memory existed in the first place. Second, one would need to have some indication that it had been inhibited. Neuroimaging research has come to the rescue to provide evidence for both of these two conditions!

An attempt to address these two issues came through use of a paradigm designed to look at the inhibition of memories, called the Think/No-Think task, which was based on the Go/No-Go paradigm we discussed in relation to response inhibition (Anderson and Green, [2001](#)). In the Think/No-Think task, individuals are taught cue-target pairs that are random associates (such as the word pair “roach-ideal”) during a training phase. They are trained on the pairs so that when given the cue, they can produce or identify the target with a high degree of accuracy, ensuring that the memory exists. Notice that because these pairs are random associations, they will likely require activation of the hippocampus if they are to be encoded and remembered, as we learned in

Chapter 9. In the next phase, the experimental phase, participants are presented with just the cue. For some cues, there is a designation (e.g., a green box around the cue) indicating that the person should try to remember the target associated with that cue. These are known as Think trials. For other cues, the designation (e.g., a red box around the cue) indicates that the person should try to inhibit the associated item from coming to consciousness. These are known as No-Think trials. Moreover, a cue appears multiple times during this phase of the experiment so that participants have multiple chances to try to retrieve the memory (in the case of Think trials) or to inhibit the memory (in the case of No-Think trials). Importantly, in this phase of the study the participants never see the target item. Rather, they are asked to exert control over the memory of that item. In the final phase, the test phase, performance is measured by giving the participants the cue and asking them to produce the item that went with it (see [Box Figure 11.1](#) for a non-verbal version of this task).



Box Figure 11.1 A neuroimaging version of the Think/No-Think task that allows researchers to determine those brain regions that are involved in inhibiting retrieval of information from long-term memory retrieval.

The task consists of three phases. In the first phase, the training phase, individuals learn cue-target (e.g., face-emotional picture) associations to a high degree of accuracy to ensure that a memory has been formed. Importantly, after this point, the individuals never see the target items again. In the second phase, there are two types of trials. On some trials, called the Think trials, a given face is shown with a green border indicating that an individual should think about the associated item. On other trials, No-Think trials, the face is shown with a red border, indicating that an individual should try to inhibit letting the associated item come into consciousness. Individuals are given multiple trials for any given face-picture pair but always in the same condition (e.g., a No Think trial). Neuroimaging during this phase is used to identify brain regions more active for No-Think trials, in which a memory must be inhibited, as compared to Think trials, in which the memory is retrieved. In the third phase, memory for each target is assessed by asking an individual to provide a short description of the item that went with the face (e.g., toilet bowl). In this way, the experimenter can determine if indeed the participant was able to effectively manipulate the memory. This level of recall is compared to targets associated with faces not shown during the experimental phase, which provide an estimate of the decay in memory for the pairs over the course of the experiment.

In such experiments, individuals recall the targets better on Think trials relative to baseline items (a set of items for which the cue is not shown in the second phase of the experiment). Conversely, they recall the targets on No-Think trials more poorly relative to the baseline trials. These two findings indicate that control can be exerted over the memory. Moreover, neuroimaging studies reveal that portions of the frontoparietal network are more active for the No-Think than Think trials during the experimental phase, suggesting engagement of control

regions (Anderson et al., [2004](#)), consistent with the idea that more control is being exerted over memories in the No-Think condition than in the Think condition.

Unfortunately, none of this tells us whether the memory has indeed been inhibited. Maybe we just had a particularly congenial bunch of participants who wanted to please the experimenter. They purposely “forget” on No-Think trials because they know that they were supposed to forget those items. Or they try harder to remember items on Think trials. While differential brain activation is observed between these two conditions, we still cannot definitively say that such brain activation is directly related to inhibiting memory retrieval.

In a study performed by one of the co-authors of this book (Depue et al., [2007](#)), we were able to provide evidence that inhibition of memory can indeed occur. To do so, we took advantage of what we know about the organization of the human brain and the power of neuroimaging. We used the Think/No-Think task in our study, but unlike prior studies, we used face-picture pairs, as shown in [Box Figure 11.1](#). We know that processing of complex visual information, such as the scenes employed in this experiment, requires portions of the ventral visual processing stream. Hence, rather than asking someone if they are remembering or inhibiting a memory, we could use activity in ventral visual processing regions as a proxy for what they were doing! When people were thinking about an item, we should observe an increase in activity compared to a baseline (in this case, just a simple fixation cross on the screen); when they were not thinking about the item, we should observe a decrease in activity below baseline in these regions. In fact, this is what we found. Notice that the decrease in activity over visual areas precludes an alternative explanation for the poorer recall of the No-Think items, which is that people are not actually inhibiting the item, but rather replacing it in their mind’s eye with some other picture. If that were the case, then activity would have been observed in ventral visual

processing regions, because they were thinking about visual information (just as on the Think trials).

At the same time, we could examine the degree to which there is activity in the hippocampus, which, as we learned in [Chapter 9](#), plays an important role in memory retrieval. Therefore, if people are really inhibiting the memory on No-Think trials, we should also observe decreases in activity in the hippocampus in this condition compared to the fixation baseline. Likewise, if memories are being retrieved on Think trials, then activity in the hippocampus should be greater compared to the fixation baseline. This expectation was also met. Thus, we demonstrated that a memory can indeed be inhibited.

Finally, this study investigated which regions are responsible for such inhibition. To answer this question, we determined which brain regions exhibited more activity for No-Think trials than for Think trials. A series of regions spanning the right middle and inferior frontal gyrus were so identified. Such findings fit with the role of the right inferior frontal gyrus in inhibitory processes and the right middle (i.e., dorsolateral prefrontal) cortex in control processes. Moreover, the higher the activity in these regions, the lower the activity in the ventral visual areas and hippocampus, suggesting that the prefrontal regions serve as the source of attentional control that modulates processing at the sites of attentional control (i.e., the hippocampus and ventral visual processing stream).

In fact, the nature of this relationship predicts how effective individuals are at inhibiting memory retrieval. Those participants who have more of a reciprocal pattern of connectivity between these prefrontal regions and the hippocampus on No-Think trials have a better ability to inhibit memory retrieval. Individuals with ADHD do not show such a reciprocal relationship. Although they can correctly remember items on the Think trials, they have a selective deficit in inhibiting memory retrieval on No-Think trials (Depue et al., [2010](#)).

This research has led to a model (Depue et al., 2012) that suggests, consistent with attentional models of top-down control, that the prefrontal cortex

down-regulates activity in the hippocampus to inhibit the overall process of memory retrieval. Said differently, prefrontal cortex is shutting down the hippocampus in general on No-Think trials rather than trying to act on the specific memory associated with a given cue. If the hippocampus is shut down, then memory retrieval will not proceed. Consistent with this idea, further research has shown that memory for “filler” trials in a modified Think/No-Think task that require neither memory retrieval nor memory inhibition are influenced by how close in time they occurred to a No-Think trial. For example, recall is worse for filler trials that follow a No-Think trial, suggesting that after inhibiting the hippocampus on a No-Think trial, it takes a while for this brain structure to ramp back up (Hulbert et al., [2016](#)).

These experiments are just one example of how cognitive neuroscience can be used to investigate issues that have fascinated clinicians and scientists for quite some time. The results may also have implications for psychiatric disorders in which recurrent memories or images are a problem, such as posttraumatic stress disorder and obsessive-compulsive disorder. For example, these disorders may be characterized by deficiencies in prefrontal control, and therapies that target these regions may turn out to be beneficial.

Higher-Order Thinking

So far we have considered executive function mainly from the perspective of guided behaviors that enable us to reach a goal. However, executive function is often conceptualized to include a set of abilities known as [higher-order thinking](#), which is a term broadly used to describe those more complicated aspects of thought, such as being able to think in an abstract and conceptual rather than concrete manner, the ability to deduce rules or regularity, and the ability to be flexible and respond to novelty. Many of these abilities require at least a subset of some of the skills we described earlier. For example, one has to be able to shift between tasks or mind sets to flexibly adapt to

changing situations or new ones. So you should not find it surprising that the frontal lobes make many contributions to higher-order thinking.

Abstract and Conceptual Thinking

One deficit exhibited by patients with executive dysfunction is an inability to process material in an abstract rather than a concrete manner. As we discussed earlier, the more abstract the conceptual task set that must be imposed, the more difficult it may be for patients to do so. For example, frontal lobe patients might be able to sort on the basis of black versus white items, but will have more difficulty sorting four-sided figures from six-side ones.

Another avenue for examining abstract thought is to identify the neural systems activated when people process metaphorical as compared to literal meaning. In [Chapter 8](#), on language, we emphasized the role of the right hemisphere in nonliteral language. Here we consider more carefully the role of frontal regions. In one neuroimaging study, participants were given three types of sentences: ones that had a literal meaning, ones that had a metaphorical meaning, or ones that were anomalous and did not make any sense. The person's task was to indicate whether he or she understood the meaning of each sentence. When reading metaphorical sentences, activity was greater in many areas of prefrontal cortex, including medial prefrontal cortex (BA 10), dorsolateral prefrontal cortex, and inferior frontal cortex, compared to reading literal sentences (Shibata et al., [2007](#)).

Another way to examine the issue of abstract thinking is to examine analogical reasoning. Analogies require a person to integrate relational information at a more abstract than concrete level. One neuroimaging study nicely illustrates this point. Researchers asked people to perform two similar tasks that differed only in the type of reasoning required (Green et al., [2006](#)). Both tasks involved the presentation of pairs of words. In the analogy task, people viewed pairs of words such as "PLANET:SUN + ELECTRON:NUCLEUS" and had to decide whether or not the two word pairs

constituted a valid analogy. This example is indeed a valid analogy, as planets revolve around the sun and an electron revolves around the nucleus of an atom. In the other condition, people decided whether the relationship between the two words within each pair was valid, and responded true if both relationships were valid. For example, they might see “DUCK:WATER + COW:MILK.” In both cases, this relationship is true – ducks live in the water and cows provide milk. Notice that although both ducks and cows are semantically related (they are both farm animals), as are water and milk (they are both liquids), these pairs do not constitute an analogy. Thus, the answer in this task could not be deduced from semantic relationships alone. The researchers observed greater activity for analogies compared to semantically related pairs in two frontal regions. The first was the left dorsolateral prefrontal cortex, which is implicated in working memory and may hold on-line the different potential relationships between items. The other was the frontopolar cortex (BA 10), which has been implicated in higher-order relational processing.

Not surprisingly, ERP evidence suggests that this type of analogical reasoning takes time, with differences between easy and difficult analogies yielding differences only in late positive waveforms between 600 and 1,000 ms post-presentation. Source localization for these components agrees nicely with that from neuroimaging studies implicating medial portions of frontal polar cortex (BA 10) as well as lateral prefrontal cortex (Qiu et al., [2008](#)).

Of course, there are a variety of different types of analogical reasoning. Some are verbal, such as the analogy described above. But in other cases, reasoning may be visuospatial in nature. As a simplistic example, one might be asked to determine whether the following two pairs are analogous: a vertical straight line and a horizontal line that meet at their ends (so as to form a corner) and a square, as compared to a semicircle and a circle. Here the first item of both pairs is half of the second item (see [Figure 11.14A](#)). Finally, in other cases, such as is measured on matrices tasks, dimensions might have to be integrated to solve the problem. For example, one might see a white circle and then an item next to it that is a white circle with a black square in

it. Then given a black square, one might have to pick out the corresponding item that would make an analogous relationship (e.g., a black square with a white circle within it) (see [Figure 11.14B](#)).

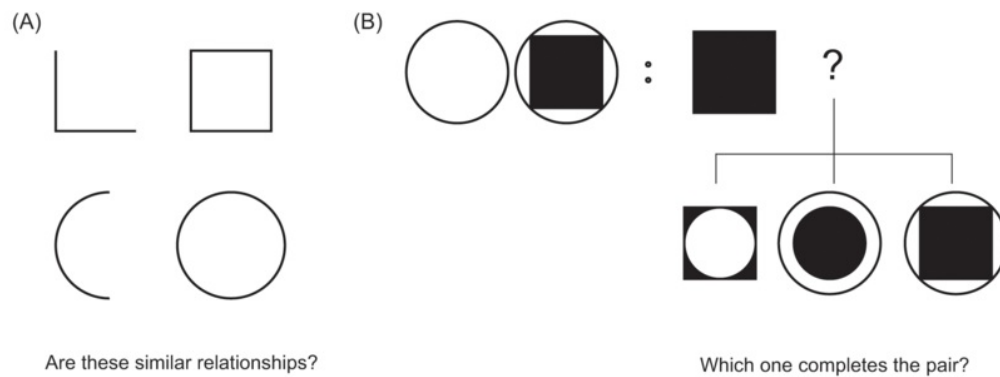


Figure 11.14 Examples of nonverbal analogical reasoning problems.

(A) A problem in which part-whole relationships must be determined. (B) A problem in which the relationship between multiple dimensions of the items must be integrated to reach the correct solution.

A recent meta-analysis has found that frontopolar and dorsolateral prefrontal regions, as well as the anterior insula and parietal cortex, are engaged during analogical reasoning, either verbal or visuospatial or when matrix problems are solved (see [Figure 11.15](#)). In addition to these regions that commonly activate for all of these types of problems, there is a distinct additional area in frontopolar cortex that activates for visuospatial analogies while a separate region activates for semantic analogies, which tend to be in a verbal format. This pattern suggests both common mechanisms for such reasoning as well as more specific regions that vary with problem type (i.e., spatial, verbal).

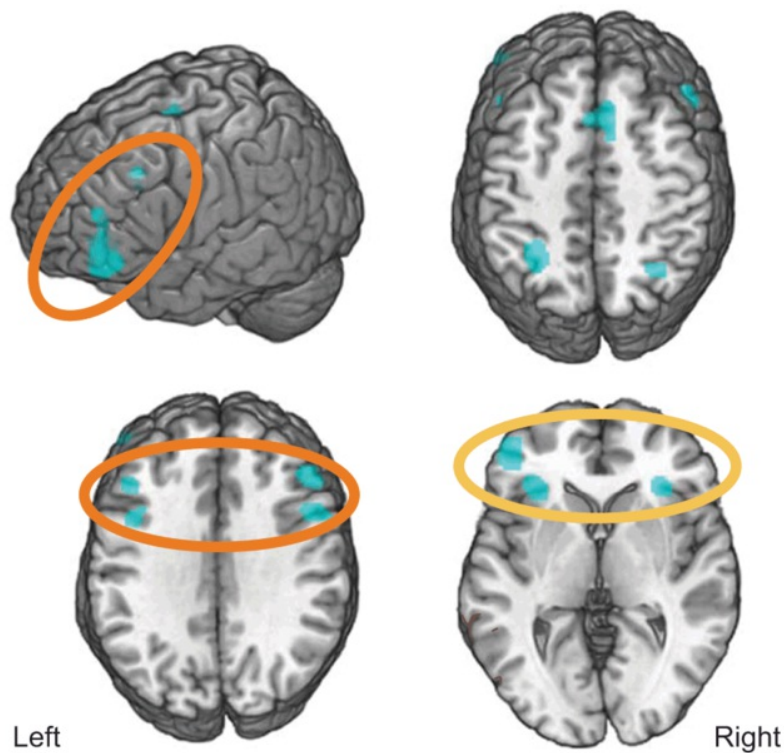


Figure 11.15 A rostralateral (frontopolar) region in the left hemisphere that has been implicated in reasoning.

Shown here are areas of the brain that are consistently activated across studies that involve reasoning, whether verbal or nonverbal. Rostrolateral regions are circled in dark orange, while anterior insula regions are circled in light orange.

(from Hobeika et al., [2016](#))

Other evidence that frontopolar as well as anterior temporal regions involved in semantic processing are important for analogical reasoning are findings that anatomical variation in these regions is associated with an individual's level of analogical reasoning (Aichelburg et al., [2016](#)). From these studies, we cannot discern cause from effect, that is, whether practice at reasoning changes brain anatomy, or whether the specific brain anatomy with which people are endowed makes analogical reasoning easier for them. Regardless, either by virtue of genetics or through sculpting by experience, morphology of these regions as well as the connectivity between them appears to help in enabling the integrative processing that is required for high-order abstract problem solving.

Rules and Inference

Another form of abstract thinking is the ability to deduce or invoke a rule. Here we consider results from monkeys, people with frontal damage and neurologically intact people. Single-cell recordings from cells in the frontal lobe of monkeys indicate that the frontal lobe contains neurons that allow for the coding of “rules.” Research has shown that neurons in frontal cortex can respond based on abstract categories, such as cats versus dogs. Unlike cells in posterior cortex that respond mainly on the basis of visual features, these cells do so with regards to more abstract criteria for categorization as they respond both to typical and atypical members of the category (Freedman et al., [2001](#)). Furthermore, the same neurons can, depending on task demands, code more than one category. More specifically, neurons that abstractly categorize cats versus dogs can, when task demands change, abstractly categorize sports cars versus sedans (Cromer et al., [2010](#)). Thus, primate frontal cortex has neurons that can encode and categorize information in a rule-like manner.

Abstraction and rule-like understanding is compromised in at least some patients with frontal lobe damage. For example, although some people with frontal lobe damage exhibit only perseverative tendencies on the WCST, others cannot even figure out the criterion by which the cards should be sorted. Because they are not given concrete instructions (e.g., sort the cards into piles based on the color of the items), they cannot determine how to perform the task. These difficulties in conceptualization are well revealed by use of a modification of the standard WCST (Delis et al., [1992](#)). In this test, the participant is given a set of six cards that must be sorted into two equal piles. Each card contains an animal’s name and a triangle placed against a background of lines. The cards are constructed so that eight possible dimensions can be used for sorting them into piles. For example, cards can be divided on the basis of whether the animal lives on land or in the water, whether the triangle is black or white, or whether the position of the animal’s name is above or below the triangle.

The difficulty that people with frontal lobe damage have on this task highlights the underlying problem in abstract conceptualization. The patients are often deficient at describing the rule by which they sort. For example, they are unable to state something to the effect of “The animals on the cards I am putting in this pile live in water, whereas the animals on the cards in this pile live on land.” Even when the examiner sorts the cards into piles, the patients cannot identify the rule used to sort the items. They also have difficulty sorting the cards into meaningful groups when given abstract cues, such as “It has to do with how these animals behave around people,” or even more concrete ones such as “These animals are ferocious or tame.”

Intriguing research with children suggests that the inability to form abstract categories may have implications for some of the other executive abilities we discussed earlier, such as task-switching. In this study, children were given a developmentally appropriate version of the Wisconsin Card Sorting Test in which they were shown trucks and flowers that could be either red or blue. On one set of trials, they were to sort by color (red, blue) and then on the next set by object (flower, truck). The researchers divided the children into whether they perseverated or successfully made the task-switch. Next they gave children novel cards to sort (e.g., houses and apples) and found that those who could make the switch were better able to generalize, suggesting that their behavior was more likely to be driven by an abstract category (e.g., shape) than by a conception of specific exemplars (flowers and trucks) (Kharitonova et al., [2009](#)) ([Figure 11.16](#)).

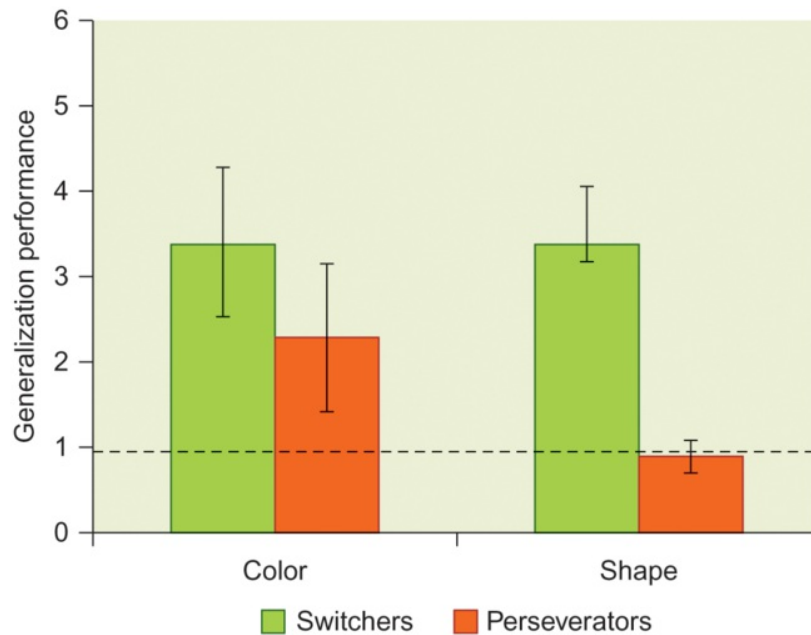


Figure 11.16 Evidence from children suggests that flexibility in task-switching is linked to the ability to maintain abstract representations of categories.

Two groups of children were identified, those who could switch between two tasks and those who perseverated. Performance of the first group is represented by the green bars, whereas performance of the latter group is represented by the orange bars. Children were then shown novel cards that like the original cards differed along the dimensions of either color or form. Switchers were more likely to generalize their sorting rule to the novel cards than were children who perseverated. Only switchers performed better than chance, which is indicated by the horizontal line.

(from Kharitonova et al., [2009](#))

Variants of the WCST modified for use in a neuroimaging environment with adults have provided insights into the neural substrates of abstract rule-governed behavior. Some studies have compared conditions in which a person is told what rule should govern his or her behavior, compared to when the person must deduce that rule. For example, in one study (Sprecht et al., [2009](#)), the participant decided whether there was a match between two nonsense symbols, presented sequentially approximately 2 seconds apart. In one condition, the person was told the dimension on which to make the decision (color, shape, or position), whereas on other trials they had to deduce the rule.

Both tasks activated a wide-ranging set of brain regions. However, much more activation was observed in dorsolateral and ventrolateral prefrontal cortex, as well as the angular gyrus, when participants had to figure out the rule by themselves rather than having it given to them.

Other research has attempted to distinguish between the ability to deduce a rule and the ability to implement a rule. In this study, researchers compared brain activity on trials in which the participant was in the process of discovering what the rule was, with trials in which participants were just implementing a rule they had previously discovered (Konishi et al., [2008](#)). More activity was observed in left superior frontal regions during rule discovery than during rule implementation.

Yet another way to examine rule-governed behavior and the ability to deduce rules is shown in [Figure 11.17](#). In this task, participants determine whether the relationship between the two items shown at the bottom of the figure is a valid inference based on the figures shown above. In this task, researchers compared inferences that could be deduced just by examining the figures above (because the same relationship was depicted above, albeit in a form that was not physically identical) or by using transitive inference (e.g., “If $A > B$ and $B > C$, then $A > C$ ”). The right lateral prefrontal cortex exhibited more activity when transitive inference was required as compared to when it was not (Wendelken and Bunge, [2010](#)).

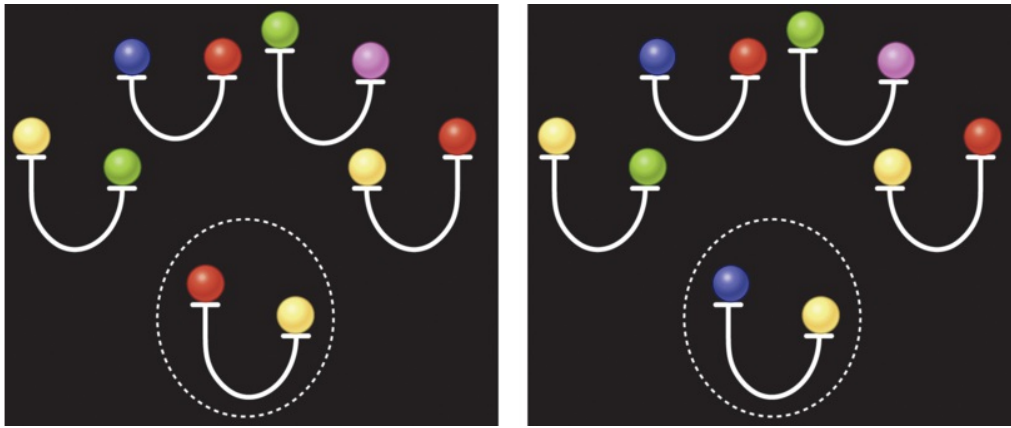


Figure 11.17 Stimuli used to demonstrate the role of prefrontal cortex in a nonverbal inference task.

Individuals decided whether the figure shown in the dashed circle represented a valid conclusion based on the figures above. Here the height of each ball represents its value compared to another. For example, the value of yellow is greater than that of green, but the value of blue equals that of red. (Left) On these trials, no inference is required, as the conclusion can be reached directly from the examples above. (Right) Here one must make a transitive inference. Because blue equals red and red is greater than yellow, one can infer that blue is indeed greater than yellow.

How can these findings be integrated? One model argues that a number of prefrontal regions, along with their interactions with posterior cortex, are required when one uses rules to guide actions. According to this model, ventrolateral prefrontal cortex, by virtue of its connections to regions of the middle temporal gyrus, plays a role in retrieving stored knowledge that allows the retrieval of rules. This suggestion is consistent with information that we learned earlier in this book implicating ventral regions of prefrontal cortex in the retrieval of semantic information and temporal regions in the storage of amodal semantic information. By this model, DLPFC is more involved in selecting or influencing how rules should be used to guide responding than in actually selecting the rules (Bunge, [2004](#)). Other viewpoints argue that DLPFC is important because it plays a direct role in abstracting the rules (Rougier et al., [2005](#)), while still others argue that DLPFC just holds rules in working memory (for a review of research on monkeys relevant to this issue, see Baxter, [2009](#)).

However, evidence from a study with patients suggests that the left lateral cortex may indeed play a critical role in rule generation. In this study, patients were tested on two different tasks: a rule generation task and a rule recognition task. In the rule generation task, participants saw two rows of six circles numbered 1–12 and had to touch the circles in a sequence that followed a rule. For example, they might touch odd-numbered circles in ascending order. For the rule recognition test, they saw a series of circles, one of which was blue. In a training phase, they learned seven different rules of how the blue circle could move in a sequence. During the test phase, they had to predict where the next location of the item would be; correct performance of this task would indicate that they recognized and understood the rule. People with damage to the left lateral frontal region as well as the medial frontal region were impaired on the rule generation test but not the rule recognition test, suggesting a role for frontal regions in abstracting rules (Reverberi, D’Agostini et al., [2005](#)). We therefore know that the ability to create and generate rules relies on a variety of frontal regions, with the dorsolateral prefrontal cortex potentially playing a prominent role.

Here we have mainly discussed problem solving from the perspective of learning a rule. Sometimes, though, we don’t deduce the answer to a problem in a linear manner. Have you ever spent time spinning your wheels trying to logically solve a problem in a step-by-step manner, only at some time in your confusion to have an “Ah-ha!” moment? This type of problem solving has been referred to as insight, and it is characterized by an obviously correct solution suddenly popping into mind. Studying this process is not easy, but researchers have done so by examining the neural signatures of problems that people self-report as being solved by insight and those solved without insight (see Kounios and Beeman, [2014](#), for review).

There is a signature state of brain activity preceding presentation of the problem that predicts whether insight is used to solve problems. First, both EEG and fMRI data indicate that prior to presentation of problems solved by insight, there is greater activity over right temporal areas associated with semantic processing and a burst of gamma

activity from this region (Jung-Beeman et al., [2004](#)). Synchronized gamma activity has been suggested as one means by which information from different brain regions can be bound together to emerge into consciousness (Tallon-Baudry and Bertrand, [1999](#)). The right hemisphere involvement in such types of problem solving should not be surprising from both [Chapters 2](#) and [8](#) in which we discussed how the right hemisphere tends to be more integrative in nature and its semantic network may allow for more diffuse and distance associations.

Second, before insight occurs there is an increase in alpha activity. This activity likely reflects increased filtering out of sensory information so that it will not interfere with the ongoing processing of a relatively weak and, as of yet, not formulated solution. By analogy, consider that when you try to solve a problem, you may close your eyes or cover your ears so as to keep sensory information from disrupting your mental efforts. Interestingly, recent studies have found that delivering anodal stimulation (which is facilitatory) over right frontotemporal cortex and cathodal stimulation (which is inhibitory) over left frontotemporal cortex regions increases problem solving on tasks that require one to “think out of the box.” The reverse pattern of stimulation has no effect (Chi and Snyder, [2011](#), [2012](#)).

Before we leave our discussion of prefrontal cortex and rules, it is worth noting some theorists’ suggestion that under certain situations we may be better off without our frontal cortex! Their argument is that the absence of frontal cortex “interference” and control frees us from the restrictions provided by the rule-based behavior we have learned, allowing and enhancing creativity. In addition, because the frontal lobes are poorly developed in children (discussed in more detail in [Chapter 15](#)), this lack of executive control may also have implications for certain developmental learning processes (Thompson-Schill et al., [2009](#)).

One dramatic example of how not having good frontal function may help in certain situations comes from a study in which people were given the matchstick problem (Knoblich et al., [1999](#)). In this problem, the person’s job is to examine an arithmetic

equation composed of Roman numerals and to move only one matchstick to make the equation true. An easy problem is one such as the following, “ $II = III + I$,” which can be made correct simply by moving a matchstick on the right of the equal sign to the left (i.e., “ $III = II + I$ ”). A more difficult problem is one in which individuals have to let go of focus on the numbers and all the arithmetic rules learned in school and focus instead on changing the operators of the equation. For example, the equation “ $IV = III - I$ ” can be made legal by moving one of the matchsticks from the equal sign to the minus sign, to yield “ $IV - III = I$.” In the most difficult problems, a matchstick in the operator not only has to be moved, but it must also be rotated (e.g., “ $VI = VI + VI$ ” becomes “ $VI = VI = VI$ ”). Amazingly, although 43% of the controls could not solve the most difficult problem, 82% of those with lateral frontal lesions did so (Reverberi, Toraldo et al., [2005](#))! Consistent with these reports, stimulation interfering with left dorsolateral prefrontal cortex increases the ability to make remote associations (Metuki et al., [2012](#)) as well as to think of novel and unusual uses for objects (Chrysikou et al., [2013](#)). What such stimulation may do is to reduce cognitive control by these left-hemisphere regions that would otherwise be involved in focusing narrowly on the most task-relevant information.

Response to Novelty

Novelty, of course, is a relative concept, but we define it here as an event, a situation, or an action that has a low probability of occurring given a particular context. Flexibility is required not only in novel situations, but also when a new reaction must be made to an old situation.

As we learned in [Chapter 10](#), the ventral attentional system is proposed to allow novel stimuli to capture attention. In fact, electrophysiological studies implicate frontal regions as playing an important role when a novel stimulus captures attention. As mentioned in [Chapters 3](#) and [10](#), an oddball stimulus that must be attended causes a P300 that is maximal over parietal regions (this P300 is sometimes referred to as the

P3b). A similar component, known as the P3a, occurs when a novel or unexpected stimulus captures attention. This component is maximal at frontocentral leads, with an occurrence 20–50 ms earlier than the P3b ([Figure 11.18](#)). For example, the P3b is elicited if an individual must count or attend to the rare beeps interspersed within a series of frequent beeps. If a totally unexpected or novel item, such as a dog bark, is inserted into the series of beeps and boops, a P3a is elicited (Courchesne et al., [1975](#)). We can be relatively certain that frontal regions of the brain contribute to the generation of this potential because (1) the P3a decreases in amplitude after lesions to prefrontal cortex (Yamaguchi and Knight, [1991](#)); (2) the amplitude of the P3a is correlated with the volume of gray matter in the frontal lobes in neurologically intact men (Ford et al., [1994](#)); and (3) high-density electrode arrays suggest a frontal source (Spencer et al., [1999](#)). Neuroimaging studies providing converging evidence that greater activity occurs in prefrontal regions in response to novel than to familiar stimuli (e.g., Kiehl, Laurens et al., [2001](#); Friedman et al., [2009](#)).

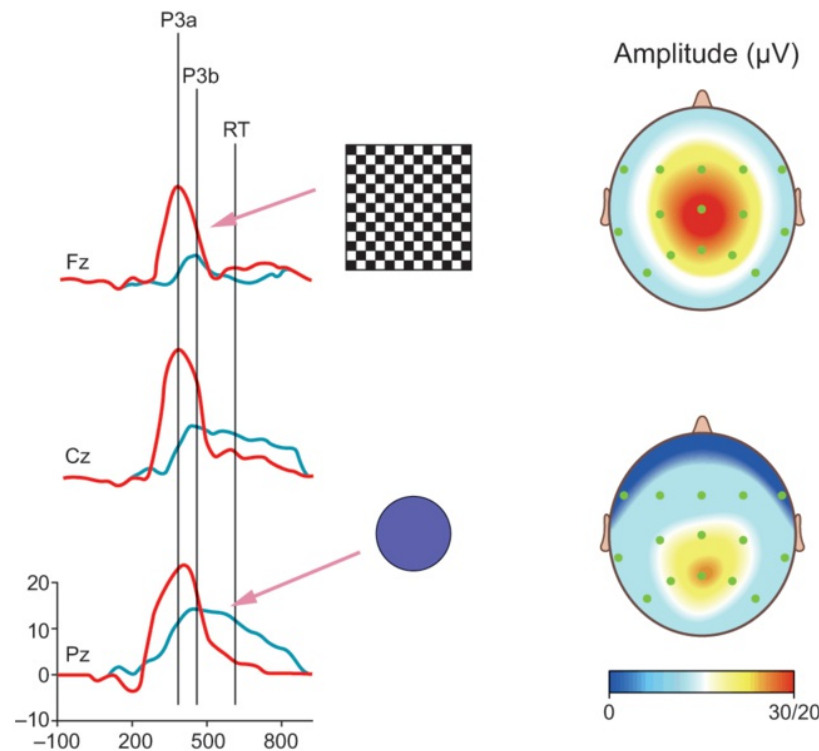


Figure 11.18 Evidence for the role of prefrontal regions in novelty.

(Left) Shown here is the response to truly novel (checkboard) stimuli (red line) and the response to rare target (large blue circle) (blue line) stimuli among a set of frequent smaller blue circles (not shown) as observed over frontal (Fz), central (Cz) and posterior (Pz) leads. Notice that the novel stimulus elicits a P3a while the rare stimulus elicits a P3b. (Right) The topography of the P3a (top row) and P3b (bottom row). Across these two panels, notice that the P3a precedes the P3b in time and has a more frontal topography than the P3b. In contrast, the P3b follows the P3a in time and has a more posterior topography.

(from Polich, [2007](#))

Not only must we detect novelty, but we also need a brain to respond in new and flexible ways. People with executive dysfunction have trouble being cognitively flexible – that is, looking at situations from a multiplicity of vantage points and/or producing a variety of behaviors (Fuster, [1985](#)). Let's discuss some examples. Patients with frontal lobe damage cannot generate alternative plans of action. Rather, they become “locked” into one way of dealing with information, which precludes the

discovery of alternative responses. On a variant of a sorting task, an individual must discover the rule for solution of a problem on the basis of the examiner's feedback as to whether each choice is correct or incorrect. Patients with frontal lobe damage will continue to act in accord with an incorrect hypothesis even though enough information has accrued to eliminate it as a viable hypothesis (Cicerone et al., [1983](#)). In part, these may be difficulties in switching set as we discussed earlier, but it also appears that their ability to conceive of a larger "search space" to explore in solving a problem is also diminished.

The tendency of patients with frontal lobe damage to start down a particular path and not consider alternative solutions is demonstrated by another task in which a series of items, such as words or pictures, must be ordered (Della Malva et al., [1993](#)). In this task, two types of trials are used. In one type of trial, two items that form a common association are presented in succession and need not be separated to form a valid sequence. An example is "sky/the/lit/full/moon/a," which should be ordered to read "A full moon lit the sky." In the other type of trial, the associated items must be separated, as in the set "of/full/the/was/coffee/cup," in which coffee and cup must be moved to correctly order the sentence to read "The cup was full of coffee." Although patients with frontal lobe damage have no trouble ordering the sentence when the associated words need not be separated, the association of two related words appears to prevent them from successfully generating a valid reordering of the words when the words must be separated.

Research across many species, including rats (Ragozzino, [2007](#)), monkeys (Petrides, [2007](#)), and humans, implicates the orbitofrontal cortex with aiding in flexible behavior. Orbitofrontal damage impedes the ability to exhibit normal [reversal learning](#), in which an individual reverses a previous response. For example, in a reversal trial, after learning to press the right-hand key when a blue light appears and the left-hand key when a yellow light appears, one would have to press the right-hand key when the yellow light appears and the left-hand key when the blue light appears. Lateral

orbitofrontal cortex, along with portions of the dorsal anterior cingulate and right inferior frontal gyrus, becomes active when one must reverse learning but not during the initial acquisition, suggesting a specific role of this region in reversal learning (Ghahremani et al., [2009](#)).

Also implicated in dealing with novel situations is the frontopolar cortex. Monkeys with damage to frontopolar cortex appear to be “hyperfocused” on current tasks, in fact, being less distracted than control monkeys when faced with distractions or free rewards. This pattern of behavior suggests that their ability to reorient potential task goals toward novel situations or opportunities is compromised (Mansouri, Buckley et al., [2015](#)). Testing of monkeys with frontopolar lesions across seven different behavioral tasks indicated that they are also impaired in learning quickly about novel rules or alternative rules, even though their prior knowledge is unaffected (Boschin et al., [2015](#)). In sum, orbitofrontal and frontopolar cortex are likely to play a large role in the control of flexible behavior.

Judgment and Decision Making

Almost any clinician who treats or works with people who have executive dysfunction will invariably report that the judgment and decision-making abilities of such people are compromised. Remember that the knowledge base of these people usually remains relatively unaffected; that is, they can retain information such as the year of Canada’s independence or the name of Henry VIII’s second wife. In some cases, such knowledge can be used effectively. These patients are as competent as patients with temporal lobe damage or neurologically intact people at judging how many clues they will need to solve a puzzle (although they don’t let such information guide their responses). Also, their estimates for judging how well they perform on concrete tasks, such as preparing meals, dressing themselves, and caring for personal hygiene, concur well with their relatives’ estimates (Prigatano et al., [1990](#)).

However, if the task becomes a bit more abstract, they begin to exhibit difficulties. For example, patients with frontal lobe damage have difficulty estimating the length of the spine of an average woman. This type of information is not usually stored in memory nor easily obtained from reference materials, such as an encyclopedia or Wikipedia. Instead, making a realistic estimate requires the use of other knowledge, such as knowing that the average woman is about 5 feet 6 inches tall (168 cm), and that the spine runs about one-third to one-half the length of the body, yielding an estimated spine length of 22 to 33 inches (56–84 cm). Patients with frontal lobe damage have difficulty making such estimates, and often state absurd or outrageous values (Shallice and Evans, [1978](#)).

Likewise, patients with frontal lobe damage are poor at estimating the price of items, such as cars and washing machines, when shown a miniature replica (which is a somewhat abstract representation of the item). In fact, they provide bizarre estimates on 25% of all responses (e.g., 10 cents for a washing machine) (Smith and Milner, [1984](#)). Their ability to estimate more abstract aspects of their own daily performance is also compromised. For example, in comparison with the ratings provided by relatives, patients with anterior lesions coupled with diffuse axonal injury grossly overestimate how capable they are of performing tasks such as scheduling their daily activities, fending off depression, or preventing their emotions from affecting daily activities (Prigatano et al., [1990](#)).

The neural underpinnings of decision making have been an especially vibrant topic of research lately (see Coutlee and Huettel, [2012](#), for review). Research in this area examines the selection of goals and actions from a somewhat different perspective than we have been discussing so far. This work tends to focus a bit more on a particular psychological phenomenon, such as how people evaluate risk versus reward or how much time people are willing to wait for a reward. Linking to the research on novelty, one of the main issues that has been examined is the issue of switching between an exploitative versus an exploratory strategy. Put differently, this is the question of “Should I stay or should I go?” Organisms are often faced with the choice of staying in

one place and exploiting the resources at that location or expending energy to explore a new locale that might potentially have greater rewards, either in terms of food, safety, sexual partners, and so forth.

The frontopolar cortex has been implicated as being particularly important for abandoning the current strategy and trying a new one, consistent with its role in processing novelty. As we will learn in more detail in the [next chapter](#) on emotion, orbitofrontal regions are thought to contribute to determining the “subjective value” that is assigned to a stimulus, whether it be food, money, a particular video game or a particularly beloved old sweater. When people decide to stick with the ongoing strategy, activation is observed in orbitofrontal regions. However, when they decide to switch strategies, activation is observed bilaterally in frontopolar cortex (Daw et al., [2006](#)). As we discussed earlier, frontopolar cortex appears to play a role in selecting overall tasks goals. As such, this frontopolar activation may potentially signal that the current task goal of exploiting the present situation needs to be reset to exploration of alternative goals or strategies.

Relatedly, frontopolar cortex appears to be able to hold information about “The road not taken” in reference to the current course of action. These ideas are well illustrated in a study in which people had to make a choice between playing one of two virtual slot machines. Over time, the probability of winning for each machine slowly changed. Frontopolar cortex appeared to track the relative advantage of switching to the other machine compared to the sticking with the current one. Furthermore, changes in functional connectivity of frontopolar cortex was observed when the switch was made, implicating this brain region as important for changing strategies (Boorman et al., [2009](#)).

Another paradigm often used to examine decision making is the delay discounting paradigm, in which an individual must decide whether they would like a smaller reward now (\$5) or a larger reward in the future (\$10 in a week). This task is sometimes also referred to as an intertemporal choice task (for review of neuroimaging and lesion

studies with this task see Sellitto et al., [2011](#)). While some researchers argue that the value of both present and future rewards are calculated by medial orbitofrontal regions (e.g., Kable and Glimcher, [2007](#)), other research suggests that dorsolateral prefrontal regions are engaged when an individual must overcome the temptation to take the immediate monetary reward (McClure et al., [2004](#)) or to choose that tasty piece of cake rather than the healthy but less mouth-watering carrot (Hare et al., [2009](#)).

Suggesting that dorsolateral regions may play an important role in overcoming yielding to the temptation of a current reward are findings that TMS over left dorsolateral prefrontal cortex biases individuals to go for an immediate reward rather than waiting. However, at the same time the subjective “value” of the rewards was not altered by TMS, precluding this as a potential reason for the more impatient behavior (Figner et al., [2010](#)). While there has yet to be a consensus on the exact roles of dorsolateral and prefrontal cortex in delay discounting, it is clear that frontal regions are important for allowing us to weigh the value of our current actions against their potential future consequences. This frontal involvement even extends to issues requiring moral judgment (e.g., Garrigan et al., [2016](#)), which we discuss in more detail in Chapter 17 (see page [538](#)).

At this point we have surveyed the neural underpinnings of a broad array of executive abilities. As should be clear, they involve a large and diverse set of frontal cortex regions. We next turn to a consideration of whether we can fruitfully conceptualize some of these regions as forming coherent, organized systems that work in a coordinated manner to exert executive control.

Organization of the Brain for Executive Function

As you should be able to tell from the discussion in this chapter, the organization of the frontal lobe for executive function is quite complicated. As we mentioned at the outset, there is unlikely to be a strict subregion-to-function mapping; rather, overlapping regions are involved in most of the functions we have described. Nonetheless,

researchers have attempted to derive some principles or general trends concerning how prefrontal cortex might be organized for executive function. We discuss a number of these in turn.

Some models focus on the organization of lateral prefrontal cortex for executive function. We will talk about two different variants, but the common element in both is that they argue for regions of lateral prefrontal cortex to be aligned along a gradient or hierarchy. One model argues that there is a nested hierarchy of control from caudal to rostral portions of frontal cortex, with the most posterior regions being influenced by the most immediate aspects of a situation and more anterior regions affected by the larger context (Koechlin and Summerfield, [2007](#)) ([Figure 11.19A](#)). This nested-hierarchy model focuses on the type of information that is used to guide control.

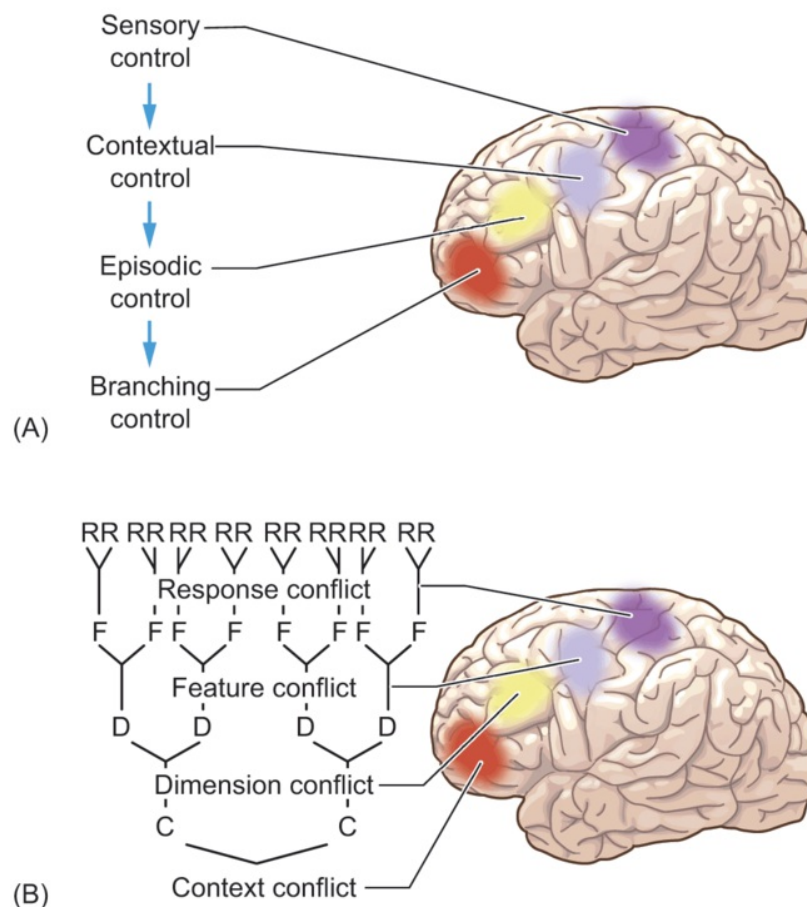


Figure 11.19 Different conceptual models of how lateral prefrontal cortex is organized for executive function.

(A) One model posits a nested hierarchy of control processes within prefrontal cortex. According to this model, there is a gradient from posterior to anterior, with more posterior regions selecting sensory information, then regions that select with regard to the context in which that sensory information occurs, then regions that select information with regard to the current episode or event, and finally regions that select with regard to the context of prior episodes or events. (B) Another model argues that selection of material occurs in posterior regions of prefrontal cortex on the basis of more concrete dimensions, and that the representations used for selection become more abstract as one moves in an anterior direction.

(from Badre, [2008](#))

This model can best be explained using an example. The one that suits our current purposes is the case of a phone ringing. Over time, you may have learned a simple

behavior: when your cell phone chimes to indicate that you've received a text, you pick it up quickly and read the text message. At this lowest level, premotor regions guide behavior based on sensory information: the phone chiming leads to a motoric response, picking up your cell phone quickly and reading the text message. If the sensory signal varies, so may the response to which your premotor region guides you. For example, if you have a different chime for your parents than your romantic interest, you may decide to wait longer to pick the phone and read the text for the former than the latter.

If responding is not constrained by sensory information, then control must be implemented at the next level by posterior lateral prefrontal cortex, which uses contextual information to guide action. For example, say your phone chimes in the middle of your cognitive neuroscience lecture (because you forgot to silence your phone). Here your posterior lateral prefrontal cortex would hopefully help you to not read the text from your romantic interest immediately because it is likely not the correct context under which to do so.

If responding is not or should not be constrained by contextual information, then control must be implemented at the next level by anterior regions of lateral prefrontal cortex, which use particular episodes to guide action. For example, say that one of your family members is undergoing surgery and your parents said that they would text you the outcome as soon as your loved one is in recovery (a specific episode). In this case, you are likely to read the text from your parents during class even though you generally don't give them highest priority and you are currently in class.

Finally, if responding is not constrained by episodic information, then control must be implemented at the highest level by the frontopolar cortex, which is thought to integrate information with regard to subgoals or specific conditions. This region helps you to consider on a more general level when it is appropriate to read texts and when it is not, allowing for different alternatives, sometimes referred to as branching control. For example, it will help you decide whether it is a good idea, while you are engaged in a conversation with someone, to look down at your cell phone immediately to read a text when the chime goes off. If your goal is to show that someone that you care about

the conversation or your goal is to absorb the information that the person is currently imparting to you, then looking down at your cell phone is not a good idea, especially under conditions in which offending them or appearing rude is likely to be deleterious to your future interactions with them. On the other hand (which is the other “branching option”), if your goal is to get you and the person to whom you are speaking to a restaurant on time, then looking down at your cell phone as soon as the chime goes off might be quite appropriate if you know that the text contains information from another friend on the fastest and easiest way to get to the restaurant. In this way, the model builds from responses selected just on stimulus characteristics to responses that are based on the current context to those that involve consideration of future outcomes.

Another model also argues for a hierarchy of processing from posterior to anterior lateral frontal regions. Unlike the prior model, however, it posits that the hierarchy is based on the nature of representations that are competing for control over action selection (Badre, [2008](#)) ([Figure 11.19B](#)). Although this is a somewhat contrived example, consider that you are trying to buy your significant other some flowers and that there are a number of different bunches of flowers in the display case that you could grab and buy. According to this model, posterior regions of lateral prefrontal cortex are involved in selecting among potential actions based on concrete stimulus-response rules. For example, you have a number of potential actions you could make, reaching to any of the different bouquets in front of you. This region could help you select the action of reaching and grabbing the bouquet that is nearest your hand, rather than reaching to any of the other locations.

Regions a bit more anterior are involved in control when the potential action must be selected on the basis of stimulus features. For example, let's say that you know your significant other really likes red flowers, so your selection of an action might be determined by which of the flower bouquets has the most reddish hue. Regions more anterior to those select on the basis of a still more abstract stimulus dimension – for example, flower family. Perhaps you know that your significant other really likes

flowers that open up over time, which would bias you to grab a bouquet with flowers like tulips, rather than a bouquet of daisies.

Finally, the most anterior regions exert control with regard to the context. For example, if it is Valentine's Day, this region would likely to help you reach for the bouquet of red roses, rather than the bouquet of crimson tulips. This model emphasizes not the temporal context, ranging from the immediate present to future, as in the prior model we just discussed, but rather the level of abstraction of information that is used to guide the selection of your action.

More recent versions of this model have posited that "abstraction" may also be represented by the number of levels that one needs to traverse to control action, that is, the depth of the decision tree. For example, more posterior regions are adequate if you have a simple two-choice mapping like "If the flowers are for my partner, get tulips; if they are for my mom, get daisies." However, more anterior regions are needed if the decision tree branches one level deeper such as "If it is not Valentine's Day then: If the flowers are for my partner, get tulips; if they are for my mom, get daisies," but "If it is Valentine's Day then: If the flowers are for my partner get red roses; if they are for my mom, get white roses" (Ranti et al., [2015](#)). While the models we have just discussed mainly focus on the organization of lateral prefrontal cortex, other models have argued that medial prefrontal cortex might also be organized in a similar manner with more posterior areas monitoring and evaluating the outcomes of actions based on more concrete rules and more anterior areas doing so for actions based on more abstract rules (Zarr and Brown, [2016](#)).

Importantly, what is common to these models is that they view control as implemented at a variety of levels by distinct regions of prefrontal cortex. They also assume that these levels are aligned along a gradient from posterior to anterior regions of prefrontal cortex, although the exact underlying dimension of the gradient (e.g., abstraction, depth of decision tree) remains a matter of debate. What such a parallel and hierarchical organization provides is the flexibility to select our behaviors and actions

in a multiplicity of manners, providing for varied manners and degrees of control. Furthermore, such an organization provides the possibility that mutual constraints on control across these different levels may help us to quickly zero in on the best option (Ranti et al., [2015](#)).

Other models focus on the relationship between lateral and medial regions. Another viewpoint of prefrontal function is that selection or control processes involve prefrontal regions that exert control at different times, from task preparation to stimulus processing to response output and then response evaluation. This model views control as implemented in a cascade involving lateral and medial prefrontal regions (Banich, [2009](#)) ([Figure 11.20](#)). According to this model and consistent with much prior research, posterior regions of dorsolateral prefrontal cortex send a top-down signal to bias activity toward those regions of posterior cortex that will be needed to process task-relevant information, essentially imposing an attentional set. This can be imposed before a stimulus is even received. For example, in the Stroop task, posterior regions of DLPFC work to bias processing toward color identification and away from word reading. More anterior regions of DLPFC help in biasing processing toward items or item attributes that are most task-relevant, such as biasing processing toward processing the information contained in the ink color of that item rather than the color named by the word. Next, posterior regions of the dorsal anterior cingulate help to bias processing toward the use of certain information to select a response, in this case ink color. More anterior regions evaluate the appropriateness of the response. Other models posit that when anterior cingulate activity is increased, it provides a signal back to lateral prefrontal cortex to increase top-down control (Botvinick et al., [2001](#)).

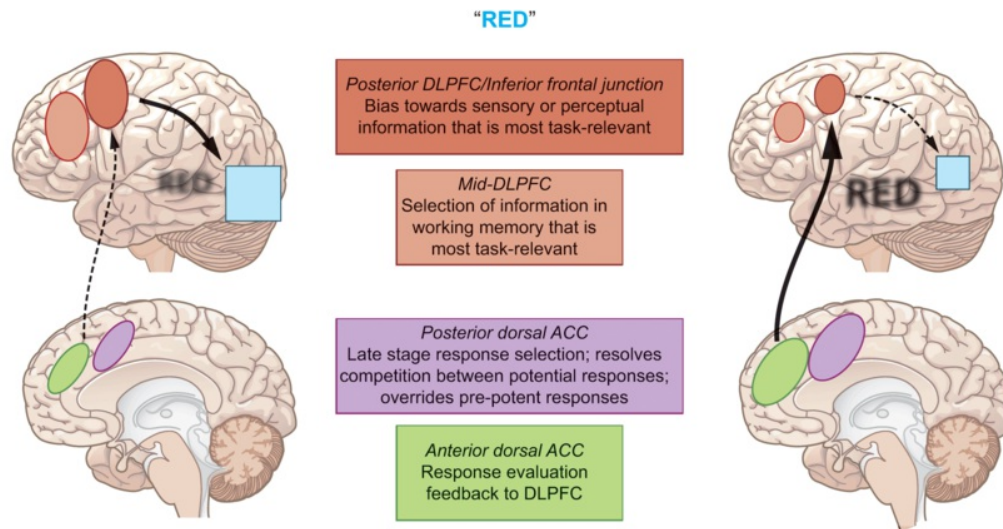


Figure 11.20 A conceptualization of how lateral and medial prefrontal regions exert executive control, from stimulus input to response output, via a cascade of control, using the Stroop task as an example (Banich, 2009).

In the Stroop task, one must identify the color ink in which a word is printed and ignore the meaning or response to which the word leads. According to this model, posterior regions of DLPFC bias an individual to the task-relevant processes carried out in posterior regions of the cortex, such as biasing toward the processing of color (represented by a square) more than to word reading (bias towards the word). Middle regions of DLPFC bias processing to the representations that are most task-relevant, such as a specific color (e.g., blue) rather than a specific word (e.g., red). Posterior regions of the dorsal anterior cingulate cortex (ACC) aid in selecting which information should guide the responses; in this case, the response linked to blue rather than the response linked to red. Finally, more anterior regions of the dorsal ACC are involved in helping to evaluate whether a response was correct. If the response was not correct, it sends a signal back to posterior DLPFC to increase control. (Left) A case in which there is good top-down control from the DLPFC indicated by large (brown and tan) ovals. Note that there is better biasing toward color processing (depicted by a larger blue square) and less so toward word reading (depicted by the word "red" in smaller font) in posterior regions. Also the "word" is less strongly represented than the color information in working memory. As such, there is not much biasing that must be done by the ACC (as indicated by small purple

and green ovals), and there is no need to send a strong signal back to the DLPFC to increase control (as noted by dashed arrow). (Right) A case in which there is poor top-down control from the DLPFC indicated by small (brown and tan) ovals, less biasing toward color in the posterior regions and in working memory. Now the anterior cingulate needs to be more activated to be able to emit a correct response, and a signal needs to be sent back to the DLPFC to increase control.

Importantly, control in this model is viewed as a cascade. If control is not well implemented at a prior “waystation,” more control will be required at the next point in the circuit. For example, if posterior dorsolateral prefrontal cortex does a poor job of imposing a top-down attention set, then it will be harder to select the correct response, which will require the anterior cingulate to work harder to select the correct response. Conversely, if the dorsolateral prefrontal cortex does a good job of imposing an attention set, then there will be reduced cingulate activity because response selection will be relatively easy (e.g., Milham et al., [2002](#); Siltan et al., [2010](#)). Future research will determine which of these models, or which portions of them, best explain how the frontal cortex actually exerts cognitive control.

What hopefully is apparent in our discussion not only here but throughout the chapter is that it is difficult to localize cognitive control and executive function to specific areas of brain tissue. Rather, what we have observed is that multiple regions of prefrontal cortex are involved in the different aspects of executive function we have discussed. Furthermore, we have observed that it is interactions between these prefrontal regions, both among themselves – anterior to posterior, medial to lateral – as well as with other regions – both cortical regions, such as the parietal lobe, and subcortical regions, such as the basal ganglia – that allow for executive control. As such, the study of executive function in cognitive neuroscience today is shedding much light on the importance of interaction between brain regions in influencing our behaviors.

A Central Role for Working Memory in Executive

Function

Before we leave our discussion of executive function, we should emphasize that, as you have seen, a substantial amount of research implicates dorsolateral prefrontal cortex across many different aspects of executive function. That point should have become obvious to you as you read this chapter. But why is that? Researchers have argued that DLPFC may play a central role in executive function because it supports working memory. This is not to say that executive function is synonymous with working memory, but rather, as outlined in psychological theories, that working memory plays a central, prominent role in executive function (see Mansouri, Rosa et al., [2015](#) for a recent review).

To better understand the link between working memory and executive function, let's briefly review some of the characteristics of working memory. As you may remember from [Chapter 9](#), working memory is a limited-capacity system that keeps information on-line for use in performing a task. How might difficulties in working memory account for some of the deficits in executive functioning? If one cannot maintain information in working memory, one may not be able to keep a goal in mind; thus, this deficit interferes with a person's ability to direct behavior toward a goal or to formulate a strategy for attaining the goal. In addition, difficulty in keeping information on-line may disrupt a person's understanding of temporal relations between items and events. If what has just happened cannot be kept on-line, its relation to subsequent happenings will be lost. In such cases, sequencing would be quite difficult. Moreover, if one is not able to retain multiple pieces of information simultaneously in working memory, there will be difficulty in creating or following rules, in making inferences, and/or in understanding the relations between items in the world. As you may remember, psychological models suggest that both the ability to hold information on-line and the ability to update working memory are very important for executive function. If one is unable to clear out what is held in working memory, perseveration will result. Accordingly, difficulties in working memory may account for a number of the those observed in cases of executive

dysfunction (for a computational model demonstrating how working memory supports executive function, see Hazy et al., [2006](#)).

In consideration of these facts, we can see that the line between two processes we have treated as distinct in previous chapters – working memory and goal-directed aspects of attentional control – is really quite blurred. If you think about it, you can see that these functions clearly are related. Working memory allows you to keep in mind your ultimate goal, as well as the type of information to which you should be attending. For example, working memory allows you to keep in mind that the goal of your foray to the shopping mall is to buy a present for your friend, and that she needs a scarf, and that purple is her favorite color.

Likewise, executive aspects of attentional control are required to determine what information is selected to be maintained or manipulated in working memory (e.g., Banich et al., [2015](#)), and which of the contents currently in working memory are most relevant for current task demands (e.g., Nee and Jonides, [2014](#)). Suppose you are at an airport listening to the announcements. Working memory allows you to keep what you've just heard in mind. However, you need to select only that information associated with your flight number or your destination. Furthermore, when the announcement indicates the gate at which your flight number is embarking, you need to select the gate number but not your destination to be maintained in working memory. Thus, we can synthesize many of the perspectives presented in this chapter by suggesting that it is the interrelationship between regions of prefrontal cortex, and the interrelationship between working memory and selection processes, that lie at the heart of executive functioning.

Before we leave this chapter, it is worth noting that there are many questions about executive function that remain to be answered and with which scientists are currently grappling. One central issue is how executive control allows us to create rules by which we exert control in a stable and consistent manner, while at the same time allowing for flexibility in our behavior (e.g., Goschke, [2013](#)). Said differently, executive control must allow us to maintain goals, ensuring stability of our actions, but at the same time

provide the ability to break and go beyond rules and current goals to adapt and act flexibly. How can a system be designed to do both at the same time? At least some research suggests that dopaminergic activity in prefrontal cortex biases control toward a more stable state, while dopaminergic activity in the striatum may bias toward a more flexible state (Cools, [2016](#)).

Another central question involves how learning interfaces with cognitive control. What is the process by which we learn to exert control? We obviously cannot have some all-knowing “homunculus” or little man sitting somewhere in our frontal lobes pulling at the levers of thoughts and actions to guide our behavior. At least some work suggests that the process of learning to exert control is developmental. Before and during the school-age years, the brain matures so as to allow increasingly active and abstract goal representations to be maintained in prefrontal cortex (Munakata et al., [2012](#)), which enables an increasing ability to exert cognitive control. And maturation of prefrontal systems during adolescence, as well as their connectivity, also appears to influence the ability to exert control (e.g., Andrews-Hanna et al., [2011](#)). That, however, cannot be the whole story, as we are faced with new situations that require control throughout our adult lives. Much current research is examining how learning mechanisms involving the basal ganglia (refer back to page [273](#), Chapter 9) may interface with prefrontal cortex to help guide and shape our ability to exert control (e.g., O’Reilly et al., [2010](#); Schiffer et al., [2015](#)). These questions remain to be answered as scientists try to discover the neural underpinnings of some of the most complex of human behaviors.

Summary

Theoretical Perspectives

- Executive functions are a series of abilities that are required to guide or control behavior toward a goal; these abilities rely heavily on the frontal lobe.
- Executive control must also be exerted in novel situations when no preexisting schemas for how to act are available to use, and when typical responses must be

overridden or inhibited.

- Some models view executive control as a unitary system, whereas others conceptualize it as having subcomponents. One set of proposed subcomponents consists of initiating and sustaining a response, setting tasks, and monitoring. Another proposed set consists of maintaining a task set, task-switching, and the updating of working memory.

Goal-Directed Behaviors

- Goal-directed behavior consists of many subcomponents, including the initiation of behavior; the creation and maintenance of a goal, plan, or set; sequencing; set-shifting; self-monitoring; and evaluation and inhibition.
- The initiation of behavior is often compromised in individuals who have frontal lobe brain damage. Behavior initiation appears to be relatively more reliant on medial prefrontal regions.
- The creation and maintenance of a goal or plan relies on many regions of prefrontal cortex, dorsolateral prefrontal cortex being prominent among them.
- The ability to sequence items also appears to rely on dorsolateral prefrontal regions.
- Set-shifting is supported by a large number of regions, including dorsolateral, inferior, and medial prefrontal regions. The regions that support this ability may vary based on task demands. For example, inferior frontal regions may play a prominent role when former task sets must be overridden, whereas dorsal regions may be more involved when task sets that must be alternated are rule-based.
- The brain has a neural system that is active in self-monitoring and evaluation of actions. This involves the medial portions of the frontal lobe and is indexed by an ERP component known as the error-related negativity.

- Some theories argue for a special mechanism of inhibitory control that relies on regions of right inferior frontal cortex, which are involved in overriding or inhibiting responses (especially when they are well learned), as well as in aborting or terminating responses. Other theories argue that inhibitory control is really just an example of when one must maintain a task set, albeit under difficult conditions or when there are competing demands.

Higher-Order Thinking

- The frontal lobes play a role in abstract and conceptual thinking, such as that required to understand metaphor or analogy.
- Implementing rules and making inferences require coordination between frontal regions and posterior brain regions where previously learned knowledge is stored.
- Frontal regions, especially the orbitofrontal cortex and frontopolar cortex, are required to flexibly exert behavior, such as changing from previously invoked plans or courses of action.
- Judgments and decisions, including those about moral dilemmas, require a contribution from frontal cortex.

Organization of the Frontal Lobe for Executive Function

- Executive function requires the coordinated activity of different portions of the frontal lobe, although certain regions may play a more important role in certain aspects of control than others.
- One prominent model argues that there is a nested hierarchy of control from caudal to rostral portions of frontal cortex, with the most posterior regions being influenced by the most immediate aspects of a situation and more anterior regions by the larger context.

- Another model also argues for a hierarchy of processing from posterior to anterior lateral frontal regions, but holds that these regions implement control based on the level of abstraction at which the conflict occurs or the level at which control must be exerted.
- Another view of prefrontal function is that selection or control processes involve prefrontal regions that exert control at different times, from task preparation to stimulus processing to response output and evaluation. This model posits a cascade of control involving the creation of a top-down set by lateral prefrontal regions and selection at a more response-based level by medial prefrontal regions.

A Central Role for Working Memory in Executive Function

- Dorsolateral regions play a prominent role in many aspects of executive function. This association may occur because this region supports working memory, which is required for many executive functions.

Chapter 12

Emotion



Subcortical Contributions to Emotion

Fight-or-Flight Response

Fear and Emotional Learning

The Amygdala's Role in Emotional Learning

Connections to and from the Amygdala

Reward and Motivation

In Focus: The Pleasure of Music

Cortical Contributions to Emotion

Representing Bodily Cues of Emotion

Integrating Emotion and Action

Incorporating Emotion into Decision Making

Regulating Emotion

Communicating and Interpreting Emotional Signals

Facial Expressions

Prosody

Models of Emotional Experience

Summary

By March 30, 1981, James Brady had been serving for several months as the press secretary for US president Ronald Reagan. Brady was known and liked by the White House press corps for his wit and energy. For example, during a lunch with reporters, he described a particular government bureaucrat as sleeping “in the closet hanging upside down with his wings over his eyes” (Bumiller, [1982](#)). But March 30 was a terrible day for Jim Brady and all those who knew him. During a gunman’s attempt to assassinate President Reagan, Brady took a bullet in the head.

The injury was very severe – in fact, at one point that evening, CBS anchorman Dan Rather mistakenly reported that Brady had died (Bumiller, [1982](#)). Eventually surgeons were able to reduce the swelling and bleeding in his brain so that Brady survived. However, because of the bullet’s trajectory, he suffered extensive brain damage to his right frontal lobe (Cytowic, [1981](#)).

Many of the symptoms that Brady experienced are predictable from what we have already learned about the frontal lobes. Brady suffered paralysis of the left arm and leg, consistent with damage to the motor regions in the right frontal lobe. He also showed cognitive symptoms of frontal lobe damage, such as difficulties with initiating action and a tendency to perseverate in his thought.

But the gunshot wound did not just affect Brady’s cognitive functions – it affected his emotional regulation and emotional state as well. In an essay, his wife Sarah Brady wrote:

[S]trong feelings of any kind could bring on what we called a “wail” – a very unnerving noise somewhere between crying and laughing. As his brain healed, he was increasingly able to control it, and in later years, he would wail only during extremely emotional moments – sad or happy – such as the singing of the national anthem. But in those early days, it happened all the time: He would start to say something, and suddenly his voice would just wail off.

At other times, though, Brady was described as speaking in a “slow, measured cadence” (De Witt, [1990](#)) that lacked the emotional inflections of normal speech.

After his injury, Brady also tended to be a bit more brutally honest than people in the political sphere are generally inclined to be. For example, he made highly unflattering remarks about some of his former colleagues in the White House, sometimes making those around him a bit uncomfortable (Bumiller, [1982](#)). Although these tendencies may simply reflect the change in outlook that accompanies a brush with death, they may also reflect a failure of his damaged frontal lobes to inhibit socially inappropriate behavior.

Despite his tragic circumstances, Brady continued to maintain his trademark wit; about John Hinckley, the man whose bullet hit him but missed President Reagan, Brady said, “I think that guy was an awfully bad shot.” During the remainder of their lives, Jim and Sarah Brady dedicated themselves to advocating against gun violence and for the recognition of people with traumatic brain injuries. While James Brady can teach us about the emotional consequences of right frontal lobe damage, he also teaches us a lesson about emotional resilience in the face of tragedy.

Imagine a day without emotion. According to the psychologist and philosopher William James, living without emotion would require a person to “drag out an existence of merely cognitive or intellectual form.” James thought this rather undesirable, arguing that “[s]uch an existence, although it seems to have been the ideal of the ancient sages, is too apathetic to be keenly sought after by those born after the revival of the worship of sensibility” (James, [1884](#), p. 194). Though emotions can be destructive, they also bring vitality to our lives; they permeate nearly all aspects of our thoughts, decisions, and interactions with other people.

This chapter surveys different components of emotion and the brain systems that are important in implementing them. First, though, we must be able to answer a basic

question: What is an emotion? It has been said that everyone knows what an emotion is until they are asked to define it (LeDoux, [1996](#)). The American Heritage Dictionary of the American Language defines emotion as “1. Agitation of the passions or sensibilities often involving physiological changes. 2. Any strong feeling, as of joy, sorrow, reverence, hate, or love, arising subjectively rather than through conscious mental effort.” At first glance, this description seems to capture our everyday sense of the concept of emotion. However, when we examine this definition more closely, we begin to appreciate the complexity of trying to understand emotion.

This definition assumes some things about emotion that still arouse heated debate in the scientific literature. For instance, what does it mean for a feeling to arise “subjectively rather than through conscious mental effort”? Indeed, much of the processing that is associated with emotion seems to occur outside conscious awareness. We may know how to describe a feeling we are experiencing, but we are often unaware of how that feeling was generated. Nevertheless, most of us would recognize that conscious mental effort can play a role in generating or maintaining emotions. Imagine, for example, the jealous lover who dwells on thoughts of his beloved in someone else’s arms, making himself more miserable in the process.

Another contentious issue is whether physiological changes in the periphery of the body play an important role in emotion. Emotional experience is associated with changes in heart rate, blood pressure, skin temperature, and electrodermal response (the degree to which the skin conducts electricity depending on the amount of perspiration). For example, imagine the emotion of fear: you probably associate it with bodily sensations such as a racing heart and sweaty palms. But are these bodily changes just a side effect of consciously experiencing an emotion, or do they in fact bring about the conscious experience? This issue has been debated ever since William James posed the question more than 100 years ago (James, [1884](#)).

A final thorny problem involves the relationship between cognition and emotion; that is, between “thinking” and “feeling.” People often assume that cognition and

emotion are independent and even mutually exclusive – that rational thought runs counter to emotional impulses, or that more thinking involves less feeling and vice versa. But when we consider the many aspects of emotion and the neural systems that implement emotion, we will see that it is often difficult to draw sharp boundaries between cognition and emotion. For example, when we recognize a person's facial expression of happiness, are we using a cognitive system that decodes visual patterns, or are we using an emotional system that categorizes stimuli as pleasant or unpleasant? Does making adaptive choices in life depend upon elaborate rational thought, or upon instinctive understanding of the dangers and rewards of different choices? When a person's attention is captured by the sound of a scream in the distance, is that an emotional or a cognitive process? Although we will learn that certain brain systems are deeply involved in emotional functions, the brain does not divide neatly into two categories of “emotional” and “cognitive” regions, just as our psychological functions cannot be sharply divided into these two categories.

When you think of all the complexities subsumed in the term emotion, it should not surprise you to learn that there is no single brain region that serves as the emotion center. Rather, many different brain regions contribute to the experiences that we call emotion, which is sometimes also referred to as affect or affective experience. Some of these brain regions are mainly concerned with specific emotions, such as fear or pleasure; others are concerned with specific processes, such as recognizing emotion in facial expressions or integrating emotion with cognitive processing. Our challenge is to work toward an understanding of how all these different brain regions work in concert to allow the full range of emotional experiences and abilities that we enjoy. This chapter focuses primarily on the emotions that most people feel every day, and it also lays the groundwork for [Chapter 14](#), which examines disorders of emotion.

Subcortical Contributions to Emotion

Many emotions are uncomfortable to experience. However, their survival value is obvious. When a person is threatened, the body needs to mobilize its resources and take some kind of protective action: withdrawal (flight), perhaps, or aggression (fight). Furthermore, these responses frequently must be made quickly. As a result, they are often made before a person has time to perform any elaborate, conscious, cognitive assessments of the situation. In our survey of the brain regions involved in emotion, we begin by discussing the subcortical regions that implement these more automatic or subconscious aspects of emotion.

As long ago as [1937](#), James W. Papez (rhymes with “grapes”) described a subcortical brain circuit involved in emotion that included the hypothalamus, hippocampus, anterior thalamus, and cingulate cortex. Paul MacLean ([1949](#), [1952](#)) later proposed that these structures are part of what was termed the [limbic system](#) (meaning “border” or “belt”), which consists of a series of structures that sit below the neocortex (see [Figure 12.1](#)). Although investigators agree that emotions depend on the limbic system, scientists’ ideas about exactly which structures constitute this system have changed over time (Rolls, [2015](#)). For example, the hippocampus, once thought to be the hub of the limbic system, plays an important role in memory functions. In contrast, the amygdala, which in the past was not identified as a key component of the limbic system, has received a great deal of attention from neuroscientists who study emotion. In this section, we consider what is currently known about the role of subcortical structures in crucial emotional functions.

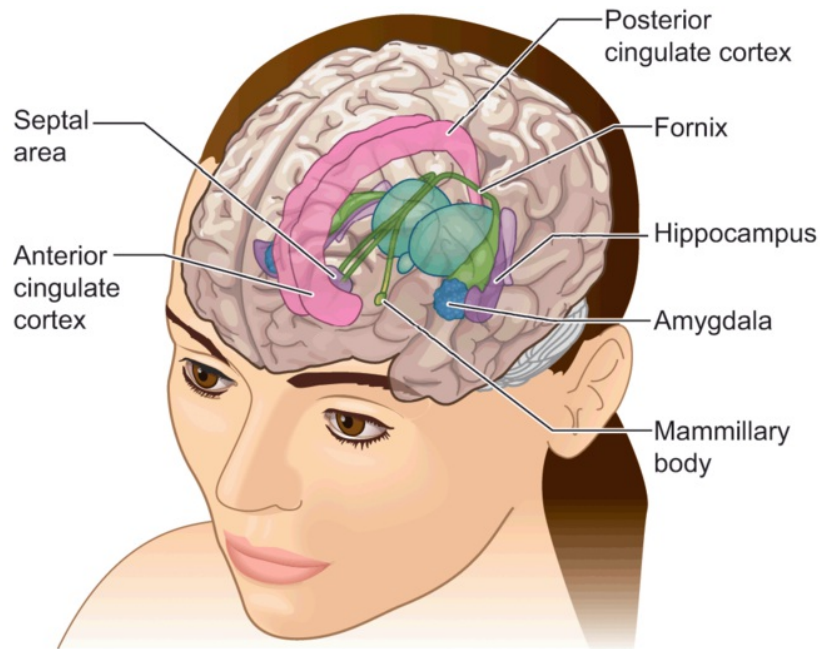


Figure 12.1 The major structures of the limbic system.

The limbic system forms a belt sitting below the neocortex, consisting of a wide variety of structures that have been implicated in emotional processing.

Fight-or-Flight Response

Emotional experiences often include bodily changes, such as an increased heart rate or sweaty palms, that are considered to be part of the body's fight-or-flight response. This response depends upon the sympathetic nervous system, a portion of the autonomic nervous system (see [Figure 12.2](#)). The autonomic nervous system consists of nerves that contact body organs such as the heart, the lungs, and the sweat glands. The hypothalamus governs the level of activity in the autonomic system, determining the extent to which the fight-or-flight response is activated. Activation of the sympathetic branch of the autonomic system causes increases in heart rate, blood pressure, respiration, and sweat secretion.

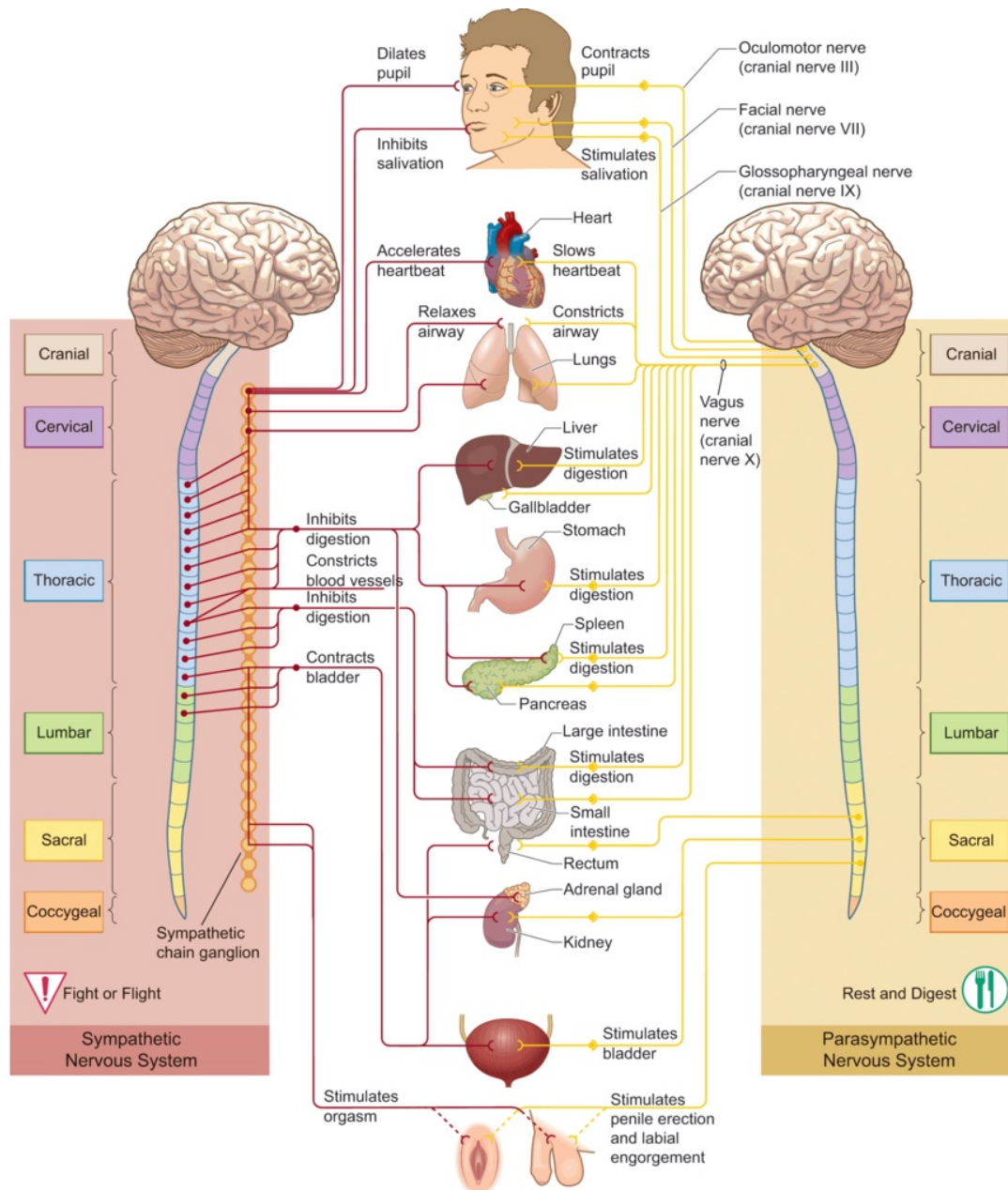


Figure 12.2 The autonomic nervous system.

Activation of the sympathetic branch of the autonomic nervous system is important in many bodily expressions of emotion, such as changes in heart rate, respiration, and sweat secretion. In contrast, the parasympathetic branch is activated under resting conditions.

The hypothalamus also controls the hormonal systems of the body. For example, through its interactions with the pituitary gland, the hypothalamus influences the level of stress hormones in the body (see [Figure 12.3](#), the HPA axis). When stimulated by the

hypothalamus, the pituitary gland releases hormones into the bloodstream. These pituitary hormones can affect target organs such as the adrenal glands, which in turn produce stress hormones like adrenaline and cortisol. Therefore, because the hypothalamus governs both the autonomic and hormonal systems of the body, it serves as an important gateway through which the brain can influence the state of the body.

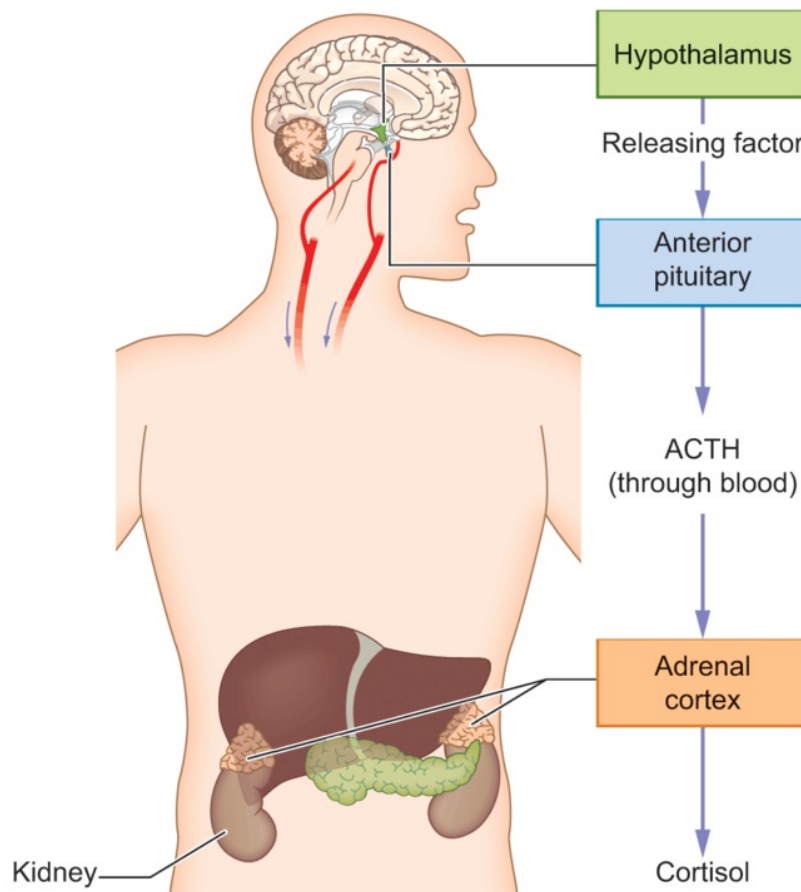


Figure 12.3 The HPA axis.

The brain controls the body's stress response through a loop that connects the hypothalamus, pituitary gland, and adrenal glands. When stimulated by the hypothalamus, the pituitary gland secretes adrenocorticotrophic hormone (ACTH) into the bloodstream, and this hormone stimulates the adrenal gland to produce the stress hormone cortisol.

So, how does the hypothalamus know when to kick the body's fight-or-flight response into high gear? How does it determine when a threatening event is present, for

example? Such decisions appear to be determined by the amygdala, another subcortical limbic region that sends its outputs to the hypothalamus. We consider the role of the amygdala in fear and other emotions in the [next section](#).

Fear and Emotional Learning

The amygdala is important for early detection of emotional information and rapid response to that information, as well as playing a role in learning the emotional significance of information (see Pessoa, [2010](#), for review). [Figure 12.4](#) shows the location and subdivisions of the amygdala. Although it is a small structure, the amygdala consists of several identifiable and interacting nuclei. Some researchers refer to this region as the amygdaloid complex, a phrase intended to capture the complicated nature of the region. Generally speaking, the basolateral nuclei project to the hippocampus and prefrontal cortex, as well as brain regions involved in reward and punishment, allowing the amygdala to influence learning and memory. The central nucleus and corticomedial nuclei connect to the hypothalamus and other brain regions involved in autonomic and hormonal responses, enabling emotional modulation of these responses (see Freese and Amaral, [2009](#), for more detailed anatomy).

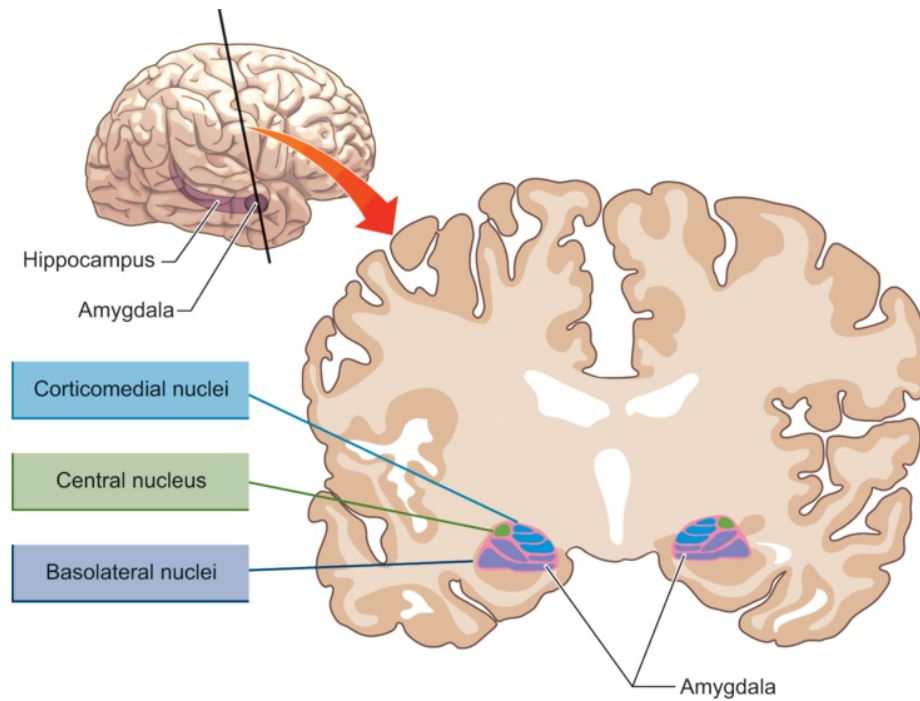


Figure 12.4 The amygdaloid complex.

The amygdala is made up of several interrelated nuclei. The basolateral nuclei project to the hippocampus and prefrontal cortex, as well as regions involved in reward and punishment, including the caudate nucleus and nucleus accumbens, allowing the amygdala to influence learning and memory. The basolateral nuclei also project to the central nucleus and corticomedial nuclei, which have a different pattern of connections. They connect to the hypothalamus and other brain regions involved in autonomic and hormonal responses, allowing the amygdala to perform emotional modulation of these responses.

Scientists first became aware of the role of the amygdala when it was discovered that large temporal lobe lesions in monkeys resulted in a set of behavioral changes known as Klüver–Bucy syndrome. These monkeys showed extremely abnormal reactions to the environment. They stopped being afraid of things they had feared in the past, attempted to engage in sexual behaviors with other species, and tried to ingest objects indiscriminately, including feces and rocks. Klüver and Bucy (1937) used the term psychic blindness to describe the disconnection between the animals' ability to process the sensory properties of objects and their understanding of the affective

properties of these same objects. These initial studies involved the removal of the entire temporal lobes, including both the cortex and the subcortical areas such as the amygdala, but subsequent research found that amygdala damage alone could produce many of these behavioral changes (e.g., Dal Monte et al., 2015; Machado et al., [2009](#)).

Lesions of the amygdala in humans also interfere with the processing of emotional information, though the effects are not as dramatic as with Klüver and Bucy's monkeys. Case studies of people with amygdala damage indicate that they lose the ability to detect aversive emotional cues embedded in visual and auditory stimuli. They have difficulty identifying fearful facial expressions as well as fearful or angry sounds (Aggleton and Young, [2000](#); Gosselin et al., [2007](#)). When such patients are asked to judge faces for trustworthiness and approachability, they rate unfamiliar photographs as more trustworthy and approachable than neurologically intact individuals do (Adolphs et al., [1998](#)). Whereas neurologically intact people can more quickly detect a threatening face in a crowd compared to a happy face in a crowd, patients with amygdala damage do not show this advantage for threat detection (Bach et al., 2015).

Neuroimaging studies provide converging evidence about the amygdala's role in responding to emotionally salient information. Activity in the human amygdala is increased in response to fearful compared to neutral faces (e.g., Dolan and Morris, [2000](#)). Not surprisingly, the amygdala is also activated in people with phobias when they are exposed to their feared object (e.g., spiders or snakes) (Larson et al., [2006](#); Phan et al., [2006](#)). Some results imply that the amygdala responds to fearful images even when those images are presented outside of conscious awareness (Whalen et al., [2004](#)), consistent with the idea that it serves as a “first alert” system in response to threats.

The Amygdala's Role in Emotional Learning

The amygdala is especially involved in emotional learning, as demonstrated repeatedly in studies of fear conditioning (LeDoux, [2014](#)). As discussed in [Chapter 9](#), in fear conditioning paradigms a neutral stimulus develops a negative emotional connotation by

virtue of its association with an aversive stimulus (see [Figure 12.5](#)). After pairing a neutral image with a very unpleasant noise, for example, people will eventually respond to the previously neutral image as if it were inherently aversive. This emotional response is reflected in physiological responses such as heart rate, skin conductance, and the startle response, which is a blink that occurs when a puff of air is blown into a person's eye.

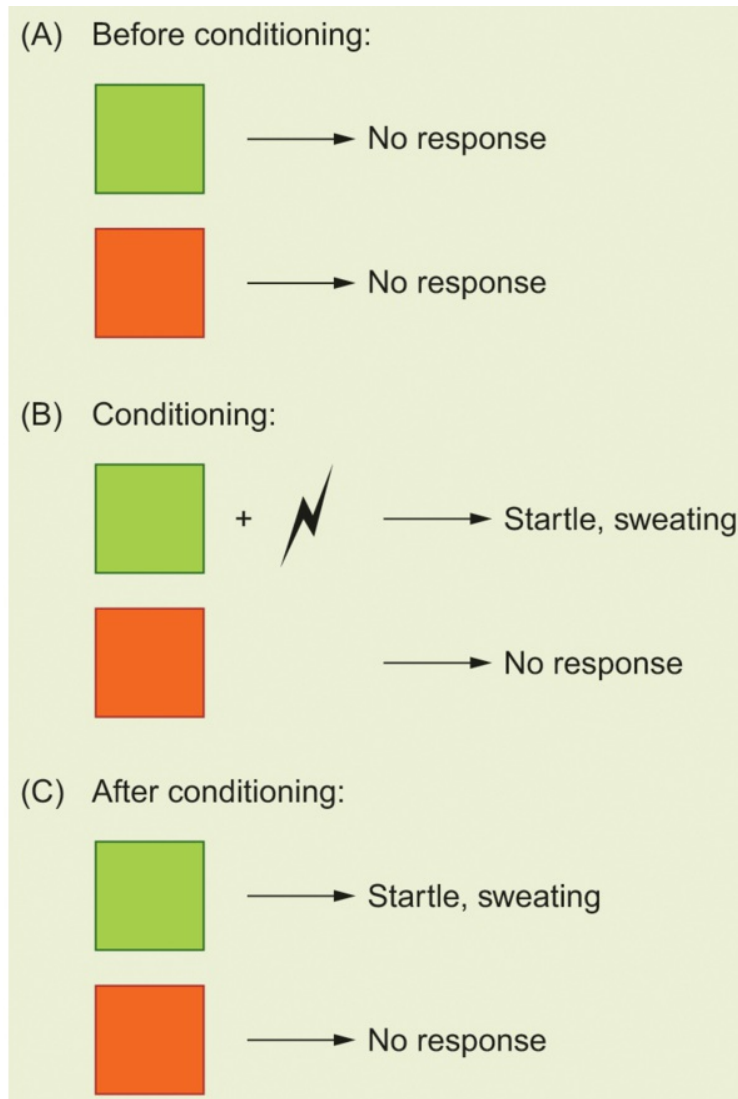


Figure 12.5 An example of fear conditioning.

(A) Prior to conditioning, an emotionally neutral item, such as an orange or green slide, does not lead to a fear response. (B) During conditioning, one neutral item, such as the green slide, is repeatedly paired with a shock, which produces a fear response including a startle reaction and increase in skin sweating. (C) After conditioning, the green slide presented alone will produce a conditioned fear response (namely, the startle and skin sweating). Damage to the amygdala impairs the ability to acquire conditioned fears.

Damage to the amygdala is known to disrupt fear conditioning in humans, as well as in other mammalian species. In one study, neurologically intact people, a patient with bilateral amygdala damage, and a patient with hippocampal damage were shown

repeated pairings of a specific color slide with an unpleasant noise (Bechara et al., [1995](#)). After conditioning, neurologically intact people reacted to the slide by showing increased skin conductance. Although the patient with bilateral amygdala damage was able to remember the pairing explicitly (e.g., “I know that the blue slide is the one with the shock”), she did not show the expected autonomic conditioned response. In contrast, the patient with hippocampal damage showed normal conditioned skin-conductance responses, but was unable to explicitly remember that the blue slide led to the shock! This is an example of a classic double dissociation, linking the amygdala with acquired fear responses and the hippocampus with explicit memory.

The amygdala is also important in learning fear through words rather than just through direct experience of an aversive consequence. For example, if you brought your hand very close to an electrical socket, you would probably show an elevated skin-conductance response, indicating activation of the sympathetic nervous system. To learn that response, you didn't need to actually stick your finger in the socket and experience the shock. Instead, you probably developed the response through verbal learning: when you were young, your parents told you not to stick your fingers in sockets.

Studies have demonstrated that this kind of verbal learning depends on the amygdala. In one experiment, participants were shown different colored squares and simply told that one specific color could be associated with a shock (although no shock actually occurred). When participants viewed that specific color, the left amygdala became activated (Phelps et al., [2001](#)). Another study found that damage to the left (but not the right) amygdala disrupted verbal learning of fear (Olsson and Phelps, [2007](#)). These studies indicate that the left amygdala is especially important in verbal learning of fear responses, which fits in well with other evidence of the left hemisphere's involvement in language.

Because fear learning is so easily studied in many species, for some time scientists tended to focus on fear learning as a model for understanding emotion more generally. However, subsequent research has found that damage to the amygdala disrupts not only

fear learning, but also certain types of reward-based learning in rodents and primates (Baxter and Murray, [2002](#); Murray, [2007](#)). Furthermore, a meta-analysis across multiple neuroimaging studies found that the amygdala responds as strongly to positive emotional information as to negative information (Sergeie et al., [2008](#)). Studies in other species, which can ascertain the microstructure of the amygdala better than human imaging studies, indicate that different subsets of cells within the amygdala are preferentially involved in aversive versus reward-based learning (Correia and Goosens, [2016](#); Janak and Tye, 2015).

One factor that can complicate any comparison of positive and negative stimuli is the arousal level of the stimuli. Negative stimuli, such as pictures of angry faces, snakes, or spiders, tend to be rated as more highly arousing than positive stimuli, such as pictures of happy faces or puppies. If negative stimuli are more arousing, then it might seem as if the amygdala responds preferentially to negative rather than positive stimuli when in fact the difference is really due to the arousal level of the stimulus rather than its positive or negative valence. Indeed, some studies have found that amygdala activity increased as the intensity level of a stimulus increased, regardless of whether it was pleasant or unpleasant (Anderson et al., [2003](#); Small et al., [2003](#)). Studies in other species have found that while some amygdala cells have valence-specific responses – responding specifically to either negative or positively valenced stimuli – other amygdala cells respond to both negative and positive stimuli in a manner that is correlated with autonomic arousal (Janak and Tye, 2015). In other words, these latter cells appear to be coding the arousal level, rather than the valence, of the stimuli.

Connections to and from the Amygdala

Given the amygdala's role in emotional learning, the brain must have some way in which sensory information from the outside world can be sent to the amygdala to enable such learning. One model proposes that two distinct pathways convey sensory information to the amygdala (see [Figure 12.6](#); Armony and LeDoux, [2000](#); see critique

in Pessoa and Adolphs, 2010). One pathway, which is important for quick, instinctive emotional responses, projects straight from the anterior thalamus to the amygdala. As you may remember from earlier chapters, the anterior thalamus is an important relay point as sensory information makes its way to the cortex. This thalamus-to-amygdala pathway can act as a “first alert” system. For example, this pathway allows a jogger to leap away from a curved shape on the trail before the conscious mind has time to think, “That might be a snake.”

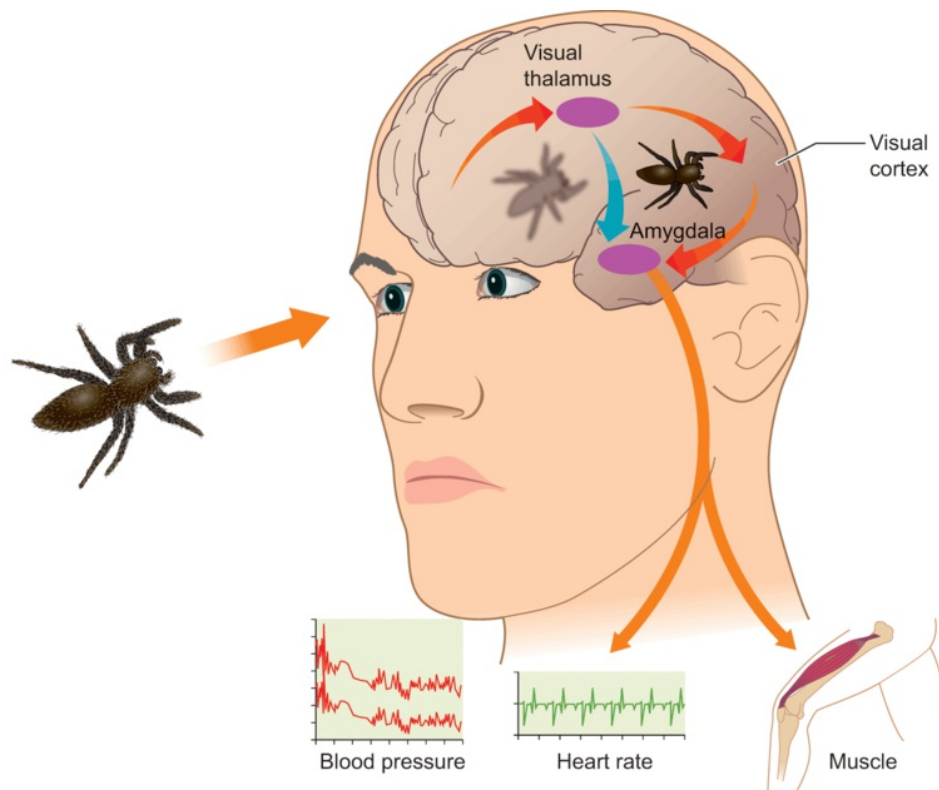


Figure 12.6 Two pathways by which sensory information reaches the amygdala.

One pathway from the thalamus to the amygdala provides basic sensory information very quickly, whereas the longer route involving the cortex provides more highly processed and detailed information. Output from the amygdala can then influence autonomic and hormonal responses. Although not depicted here, the amygdala can also influence how incoming sensory information is processed through backward projections from the amygdala to cortical regions.

The second pathway in the dual-pathways model connects the sensory areas of the neocortex to the amygdala. This pathway provides a more comprehensive context for processing emotional information. For example, after leaping to safety, the jogger might study the shape more carefully and realize that it is only a stick, not something to be feared. Thus, the amygdala appears to receive a progressively more complete image of the same information, much like a fade-in shot in the movies that becomes progressively clearer and more focused with time. The thalamo-amygdaloid pathway carries a crude, preliminary sketch of some basic properties of the stimulus – not enough to clearly identify the object, but enough, perhaps, to ready or initiate a response. In contrast, the cortico-amygdaloid pathway, which is slower because it involves more synapses, delivers enough information to give rise to an affective reaction that takes into account the complexity and details of the situation.

This model emphasizes how incoming sensory information can influence the amygdala. When the amygdala registers something fearful or frightening, though, it is important for that information to be taken into account by other brain regions. This is accomplished by additional connections running in the opposite direction from the amygdala to the cortex. These back-projecting fibers allow the amygdala to influence how attention is directed to different aspects of sensory information as they are processed by the cortex. Once the amygdala identifies an image as threatening or otherwise emotionally urgent, it can tell the cortex to pay more attention to that image. In neurologically intact people, attention tends to be captured by emotional stimuli (for reviews, see Compton, [2003](#); Vuilleumier, [2005](#)), but patients with amygdala damage do not show such attentional effects (Anderson and Phelps, [2001](#); Bach et al., 2015).

The amygdala also interacts very closely with another important subcortical structure, the hippocampus. As we reviewed in [Chapter 9](#), the hippocampus is crucial in encoding new information into long-term memory storage and in consolidating that information in memory over time. Close bidirectional interactions between the hippocampus and the amygdala allow them to influence one another's activity in several ways (for reviews, see Maren et al., 2013; Phelps, [2004](#)). For example, input from the

amygdala to the hippocampus can allow the emotional meaning of a stimulus (coded by the amygdala) to influence the encoding and subsequent consolidation of that information by the hippocampus.

Through its connections with the hippocampus and other regions, the amygdala plays an important role in remembering events that are emotionally charged (Paz and Pare, [2013](#); Yonelinas and Ritchey, [2015](#)). Generally, the greater the emotional intensity associated with an event or experience, the better it is remembered, a phenomenon known as the memory enhancement effect. Amygdala damage interferes with this memory enhancement effect (e.g., Adolphs et al., [1997](#), [2005](#)). Because the amygdala is well connected to pathways critical for learning and memory, including the hippocampal complex and striatum, it is able to increase the efficiency of learning in these networks under emotionally charged conditions. For example, a pharmacological manipulation that reduced connectivity between the amygdala and hippocampus led to a reduction in the memory enhancement effect (Alkire et al., [2008](#)). Emotion not only enhances the initial encoding of memories, but it also makes memories less prone to decay over time, that is, less prone to forgetting. Recent studies have found that synchronous interactions between the amygdala and prefrontal regions appear to account for the resistance of emotional memories to extinction (Livneh and Paz, [2012](#)).

In sum, while it is clear that the amygdala plays an important role in responding to salient emotional events and in emotional learning, we also know that it does not work in isolation (Pessoa and Adolphs, 2010). Rather, the amygdala's unique role in emotional functions comes about by virtue of its interactions with interconnected brain regions. These brain regions include higher-level areas involved in perception and memory, such as the sensory cortices and hippocampus, as well as lower-level areas that implement the fight-or-flight response, such as the hypothalamus. Interestingly, patients with bilateral amygdala damage can still experience a wide range of emotions, including fear and panic, reminding us that the amygdala does not account for all of our emotional experience (e.g., Anderson and Phelps, [2002](#); Feinstein et al., [2013](#)). For these reasons, we should be careful not to think of the amygdala as the sole "emotion

center” in the brain, or even the “fear center,” despite its important contributions to emotional processes.

Reward and Motivation

Just as identifying potential dangers is important for an organism’s survival, it is equally important for the brain to signal what situations and actions lead to rewards. Classic work on the neural basis of reward and positive motivation dates back to the 1950s, when Olds and Milner ([1954](#)) carried out experiments demonstrating that electrical stimulations to certain parts of the brain were “rewarding” for a rat. But what do we mean when we say the rats found the stimulation “rewarding”? The rats would press a lever hundreds and hundreds of times to activate a current that stimulated specific brain regions. Because the rats were willing to work so hard for this stimulation, the researchers inferred that it was rewarding. The areas where stimulation is most rewarding are the dopaminergic pathways stretching from the ventral tegmental area of the midbrain to a cluster of cells in the basal forebrain known as the [nucleus accumbens](#) (see [Figure 12.7](#)). This region is also referred to as the ventral striatum, because it is the ventral part of the basal ganglia (striatum).

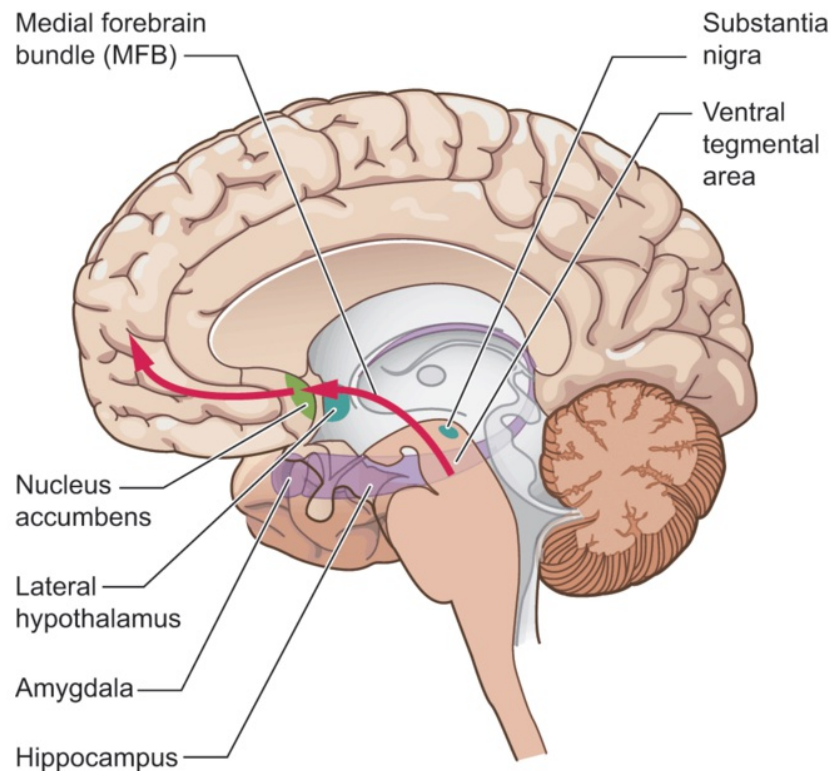


Figure 12.7 The location of the nucleus accumbens.

The nucleus accumbens receives ascending dopaminergic input from the ventral tegmental area.

It is tempting to refer to the reward pathway as the “pleasure center” of the brain, but caution is required. Just because an animal presses a lever repeatedly for stimulation, does that mean the animal gets pleasure from it? It is important to dissociate “wanting” something from actually “liking” it. This distinction is clear in research on addiction, which has demonstrated that addicts may go to great lengths to obtain a drug (i.e., wanting it), but no longer experience pleasure once they take it (i.e., liking it; Robinson et al., [2015](#)). Some researchers have proposed that the dopaminergic path leading to the core of the nucleus accumbens is not responsible for pleasure itself, but for the “wanting” aspects of reward-related behavior – those aspects that propel an animal toward desired goals (Berridge and Robinson, [1998](#), [2003](#)). In contrast, only a certain part of the nucleus accumbens – specifically, a layer of cells surrounding the accumbens and referred to as the nucleus accumbens shell – is thought to underlie the sensation of consummatory pleasure upon achieving a desired goal; that is, the “liking”

(see [Figure 12.8](#)) (Berridge, [2003](#); Castro and Berridge, [2014](#); see also Baliki et al., [2013](#)).

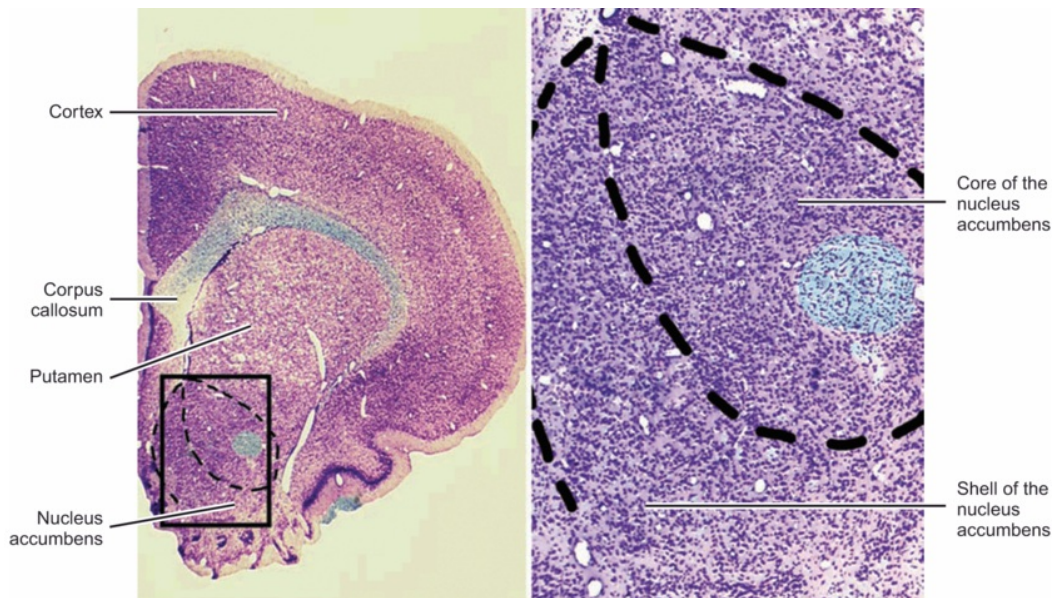


Figure 12.8 The nucleus accumbens core and shell regions in the rat brain.

The core of the nucleus accumbens is thought to play a role in wanting or desire incentive, whereas the shell is thought to play a role in consummatory pleasure.

Courtesy of Harold Prüss.

Many studies of the reward pathways have focused on nonhuman animals, but neuroimaging studies have also examined the conditions that activate the nucleus accumbens in humans. The accumbens becomes activated in people when they receive a reward, especially when the reward is unexpected (Berns et al., [2001](#)). In situations with predictable rewards, the accumbens is activated when the person anticipates the reward before actually receiving it (Knutson et al., [2001](#)). These results suggest that the accumbens is initially sensitive to unexpected rewards; however, as a pattern of rewards emerges, the accumbens begins to anticipate the reward (see also Fiorillo et al., [2003](#); Hollerman and Schultz, [1998](#)).

Evidence generally indicates that there is one basic brain system that processes rewards, regardless of the specific nature of those rewards (Berridge and Kringelbach, 2015). For example, the nucleus accumbens is activated by a variety of stimuli that

could be considered rewarding, such as sweet juice, money, and attractive faces (e.g., Aharon et al., [2001](#); Berns et al., [2001](#); Kampe et al., [2001](#); Knutson et al., [2000](#)). This region is also activated by rewarding items that are addictive. For example, smokers show greater accumbens responses to smoking-related imagery than do nonsmokers (David et al., [2005](#)). For obvious reasons, clinically oriented research on the ventral striatum has centered on its role in addiction, to which we will return in [Chapter 14](#).

While the nucleus accumbens is most widely known for its role in reward processing, evidence suggests that, once again, a simplistic view is not consistent with all the evidence (Floresco, [2015](#)). Instead, we should appreciate that the nucleus accumbens is well positioned to connect information about reward incentives to action systems. Intuitively, this makes sense: we don't just feel craving for desirable chocolate, but this desire leads us to get up and root around in the cupboard until we find a tasty morsel of it. Through its anatomical connections with subcortical motor systems, specifically the basal ganglia, the nucleus accumbens aids us in reward-seeking, that is, in acquiring the desirable objects or experiences that meet our needs. Current evidence suggests that the nucleus accumbens is particularly important in biasing behavior toward seeking desired goals when obstacles arise or when there are many options from which to choose. Thus, the nucleus accumbens might not be necessary in enabling you to reach for a chocolate that is right in front of you, but it might prompt you to seek out the chocolate that is hidden on a top shelf, or to choose the chocolate from among the many other– but less delicious – options in your refrigerator.

In Focus: The Pleasure of Music

What makes music so enjoyable to hear? No matter your specific musical preference or cultural upbringing, there is likely to be some kind of music that brings you pleasure. That pleasure may take the form of a transcendent state of bliss while listening to a classical piano concerto or a joyful urge to get up and move to your favorite dance tunes. Regardless, there is no doubt that music has a

direct path to our emotions: it can bring us up out of our doldrums and connect us to something beyond ourselves. Studies of music cognition suggest that the temporal patterns of music – the rhythmic and melodic expectations that music establishes – can explain its pleasurable properties in part (Salimpoor et al., [2015](#)). Interestingly, even people who have great difficulty accurately perceiving musical pitch can still identify the emotions conveyed by music, perhaps because they can extract music's temporal patterns (Gosselin et al., [2015](#)).

Cognitive neuroscience studies further help us to understand how the interaction between auditory and emotion-related areas of the brain can facilitate the pleasure of music. First, recent research has detailed with high precision the ways in which music activates the temporal lobe regions involved in auditory processing. Participants in one fMRI study listened to a set of 165 different sounds, some of which were speech sounds, others which were either instrumental or vocal music (e.g., guitar, pop song), and others that were familiar sounds that were neither speech nor music (e.g., siren wailing, cell phone vibrating, water splashing; Norman-Haignere et al., [2015](#)). Researchers then applied a sophisticated computational analysis which, by examining profiles of activity across all voxels in the primary and secondary auditory cortex, identified clusters of voxels consistently activated by certain kinds of sounds. One cluster was specifically activated by speech and another was specifically activated by music.

To better understand the power of music to bring us pleasure, we need to consider how these auditory regions representing music interact with the brain's reward pathways. Music – especially music that we like – activates these reward pathways, specifically the nucleus accumbens (Koelsch, [2014](#)). Further linking musical pleasure with the reward system, one study found that dopamine release increased synchronously with participants' peak emotional reactions to music (Salimpoor et al., [2011](#)).

Putting these two lines of research together, a recent study examined connectivity between the auditory cortex and nucleus accumbens while people listened to music that differed in its level of pleasantness to the participant (Salimpoor et al., [2013](#)). After listening to unfamiliar musical segments, the participants indicated how much money they would pay for the music; in this way, researchers had an objective measure of the desirability of the music. Music deemed more desirable was associated with greater activity in the nucleus accumbens compared to music deemed less desirable. Moreover, when participants listened to music that they were willing to pay more money to hear, there was greater functional connectivity between the nucleus accumbens and auditory cortex. Thus, when you are listening to music that makes you feel happy, the cortical regions representing the auditory perception of that music are likely to be more in synchrony with the subcortical regions that represent its high reward value.

Of course, music doesn't only make us feel happy, but rather it can evoke other emotions as well. For example, the music played during a scary scene in a movie contributes to the viewer's feeling of suspense and fear. Frightening music, just like fearful faces and other threats, can activate the amygdala. Interestingly, one study found that participants' amygdala responses to scary music were especially correlated with their amygdala responses to scary vocalizations such as screams, suggesting a common basis for responding to auditory representations of threats (Aubé et al., [2015](#)).

Emotions evoked by hearing music have been associated with changes in activity in a wide range of other regions as well, including the hippocampus, orbitofrontal cortex, and even motor regions of the brain (Koelsch, [2014](#)). Music can color and strengthen our memories, perhaps related to hippocampal activity. Nostalgic responses to music typically involve pleasant emotions associated with autobiographical memories (e.g., Barrett and Janata, [2016](#)). For example,

hearing a certain ballad may remind you of your first love interest, even if that was years in the past. In this case, the ballad will not only elicit a feeling, but will also lead to recall of specific memories, perhaps accounting for associated activity in both limbic and frontal regions. Music can also make us want to move (perhaps accounting for motor area activity)! For all these reasons, it makes sense that the pleasures evoked by music can affect brain activity not only in auditory and reward regions, but in networks of interconnected regions that together represent complex experiences.

Cortical Contributions to Emotion

We now turn our attention to the functions of cortical regions in emotional processes. The cerebral cortex is crucial for emotional functions such as deciding whether a particular behavior is likely to lead to a positive or negative outcome, inferring the feelings of others based on facial expression, and using the correct tone of voice to convey to others how we are feeling. Cortical regions are also important in representing bodily signals of emotion, as we will soon learn.

Representing Bodily Cues of Emotion

More than 100 years ago, the pioneering psychologist William James argued that conscious experience of an emotion depends upon the ability to mentally represent the state of the body. According to James, bodily signals provide the brain with information about the emotion that the body is experiencing, and therefore give rise to conscious emotional feelings. The finer points of James's theory have long been debated (see Ellsworth, [1994](#)). Although researchers disagree about whether it is absolutely necessary for the brain to receive information from the rest of the body before a person can feel an emotion, it is true that our minds are able to represent our bodily states in some way. For example, you might be able to tell that you are anxious because you can perceive that your heart is beating very fast.

It is important to distinguish between the control of bodily states of emotion and the ability to represent those states mentally. As already discussed in an earlier section, the hypothalamus is involved in regulating autonomic functions. For example, through the autonomic nervous system and the HPA axis, the hypothalamus can control whether heart rate is high or low. In contrast, the ability to perceive and represent the internal state of the body, a function known as **interoception**, appears to depend upon another region, the insular cortex (or insula) (Craig, [2002](#), [2009](#); Verhagen, [2007](#)).

The insula is tucked deep inside the Sylvian fissure, and it consists of three functionally distinct subregions (see [Figure 12.9](#)). According to a study of resting-state functional connectivity (Deen et al., [2011](#)), the human insula's posterior portion is functionally connected to primary and secondary motor cortex and somatosensory cortex. In contrast, anterior portions of the insula are more functionally connected to the anterior cingulate cortex: the dorsal anterior insula is connected to portions of the anterior cingulate important for cognitive control, while the ventral anterior insula is connected to portions of the anterior cingulate that are especially relevant to emotional processing (see also Chang et al., [2013](#); Uddin et al., [2014](#)). More generally, researchers have proposed that posterior insular regions represent primary sensory representations (such as taste) and more anterior insular regions integrate these sensations with awareness (Craig, [2009](#); Gu et al., [2013](#); Taylor et al., [2009](#)).

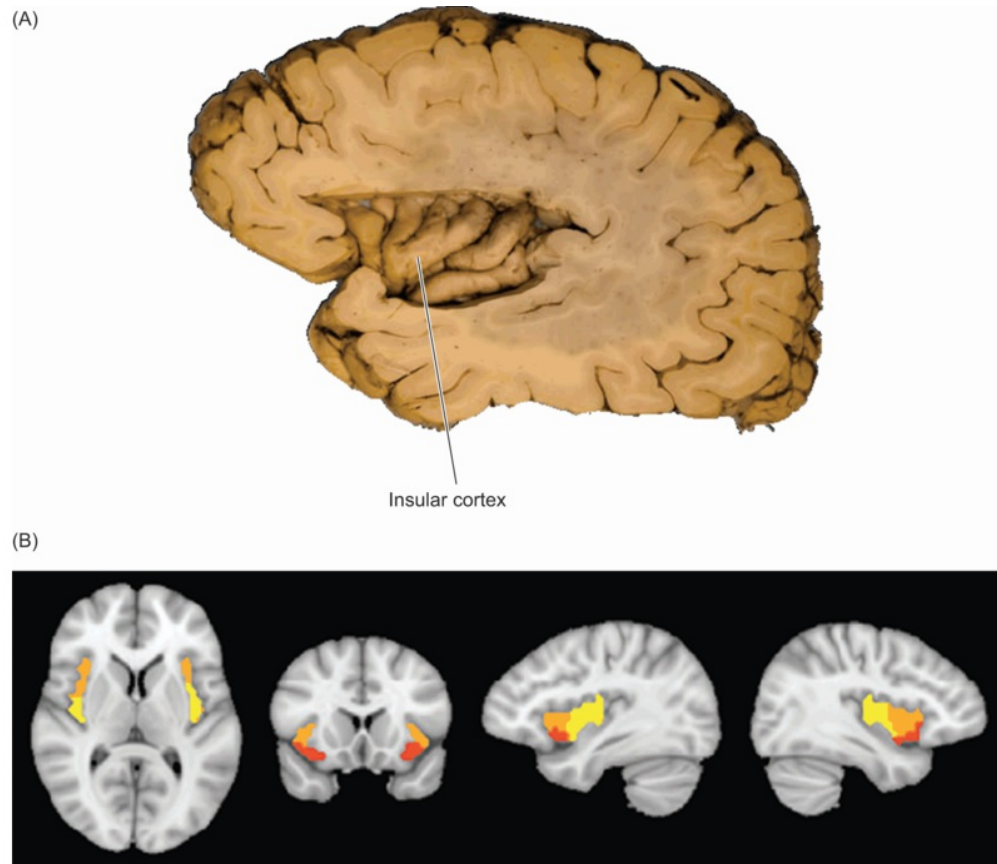


Figure 12.9 Location of the insula.

The insula is a cortical region tucked between the frontal and temporal lobes. In Panel A, a lateral section of the brain has been dissected away to reveal the insula.

Adapted by permission from Macmillan Publishers, LTD. Figure 1 from Craig, A. D. (2009). How do you feel now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, 10, 59–70. Panel B illustrates the subdivision of the insula into three components (posterior insula = yellow; dorsal anterior insula = orange; ventral anterior insula = red). (from Deen et al., 2011)

The anterior insula appears to be critically involved in representing the body's internal states. One study of the insula's role in interoception examined participants' ability to detect their own heartbeats (Critchley et al., 2004). The researchers found that activation was enhanced in the anterior insula during this task, compared to a control condition that involved detecting external stimuli (see Figure 12.10). In addition, people who were more accurate at detecting their own heartbeats had a right anterior insula that

was both bigger and more active compared to people with poor accuracy at the task. These data imply that the insula plays an important role in encoding interoceptive cues.

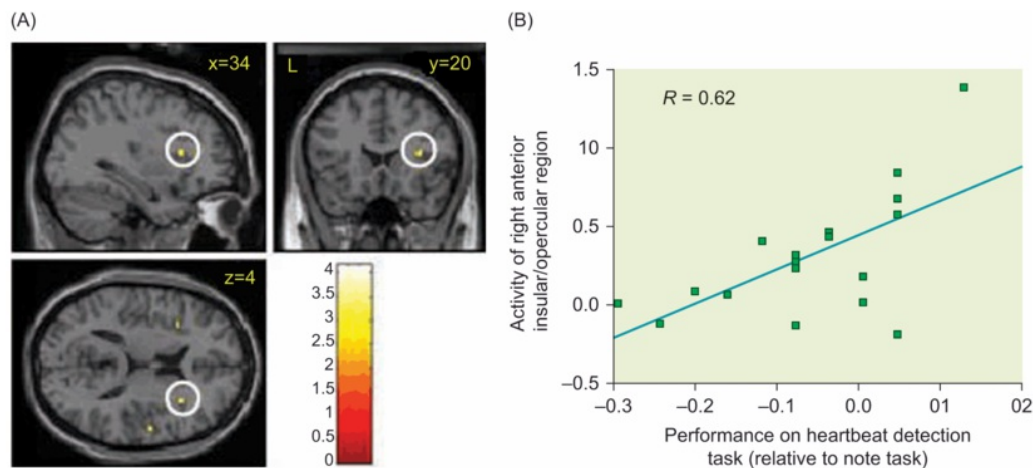


Figure 12.10 Activation of the insula during an interoceptive judgment task.

Participants had to determine whether a series of tones matched their own heartbeat. Those who performed better at the task (compared to performance on a control task involving detection of notes) had more activity in the right insula. Panel A shows the right insula region (in white circle) and panel B shows the correlation between activity in that region and performance.

Source: Adapted by permission from Macmillan Publishers, LTD: from Critchley, H. D., Rotshtein, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7, 189–195.

Whereas some research indicates that the insula is important in representing a variety of internal bodily cues of emotion, other research emphasizes its special role in the emotion of disgust. Interestingly, research with nonhuman primates indicates that part of the insula serves as the primary gustatory (taste) area. What does taste have to do with emotion? One clue is provided by the term disgust, which literally means “bad taste.” Though disgust is a sensation that we associate with rotten food or foul odors, the term has broader significance as well. As Charles Darwin noted, the facial expressions we make in situations of moral repulsion are the same as those we make when recoiling from disgusting food (Darwin, 1873). Researchers have confirmed

Darwin's observation by demonstrating that the same facial expression muscles (levator labii muscles) were activated when people tasted unpleasant liquids, viewed photographs of contaminants such as feces or insects, or experienced unfair treatment in a social game (Chapman et al., [2009](#)).

Several lines of research link the insula to disgust. Early studies performed during brain surgery found that stimulation of the insula in humans elicited sensations of unpleasant taste and nausea (Penfield and Faulk, [1955](#)). Neuroimaging studies show that this area is sensitive to processes related to feeding, such as odor, taste, tongue stimulation, swallowing, thirst, and hunger (Small et al., [2001](#)). Damage to the insula interferes with both the experience of disgust and the ability to recognize facial expressions of disgust in others (Calder et al., [2000](#); Woolley et al., [2015](#)). Likewise, neuroimaging studies have demonstrated activity in the anterior insula when the participant tastes bitter liquids, imagines disgusting scenarios, or sees another person expressing disgust (Deen et al., [2011](#); Jabbi et al., [2008](#)). Additional neuroimaging studies have shown that activity in the insula is correlated with subjective ratings of disgust (e.g., Schienle et al., [2008](#); Stark et al., [2007](#)). Tying this research together with the broader role of the insula in emotional awareness, it may be that the insula originated as an area that represented taste sensations, but then expanded to represent other bodily signals of emotion, such as heart rate, temperature changes, pain, and visceral sensations.

In humans, the insula may play a role in even more complex and abstract emotions. For example, one study found that the insula was active when participants imagined a personal event involving the most guilt they had ever experienced (Shin et al., [2000](#); see also Michl et al., [2014](#)). Although there is clearly not a "guilt center" in the brain, feelings of guilt may involve some of the same interoceptive cues as sensations of disgust, nausea, or other bodily displeasure.

Interestingly, the anterior insula's volume is disproportionately large in the human brain compared to the brains of other primates (Bauernfeind et al., [2013](#)). Furthermore,

the anterior insula in humans and great apes contains special kinds of neuron, called von Economo neurons, which are large cells with the capacity for rapid, long-range integration of information (Allman et al., [2011](#)). Only smaller-scale versions of these neurons exist in other primate species such as macaque monkeys (Evrard et al., [2012](#)). These findings fuel speculation that relatively recent evolutionary developments in the anterior insula may have allowed for the enhanced integrative capacity to support more sophisticated interoceptive awareness in humans and great apes.

Integrating Emotion and Action

As we have learned, certain subcortical regions play a role in motivated behavior. For example, the subcortical reward pathways are crucial in responding to positive incentives. And the amygdala aids in some basic reactions to emotional signals, such as freezing or beating a quick retreat from that curved object situated in the middle of the jogging path. But building upon that more automatic system, another brain structure, the cingulate cortex, appears to be crucial in evaluating the utility of actions that have emotional significance and in integrating motivational aspects of behavior.

The cingulate cortex has been viewed as a component of the limbic system since Broca first described le grande lobe limbique in 1878 (for a review, see Allman et al., [2001](#)). The cingulate wraps around the corpus callosum like a collar, or cingulum (see [Figure 12.11](#)). Traditionally, it is divided into two regions: the anterior cingulate cortex, forward of the central gyrus, and the posterior cingulate cortex, behind the central gyrus. Current research suggests that the cingulate cortex has an intricate organization with as many as nine or more distinct subregions (Beckmann et al., [2009](#); de la Vega et al., [2016](#)).

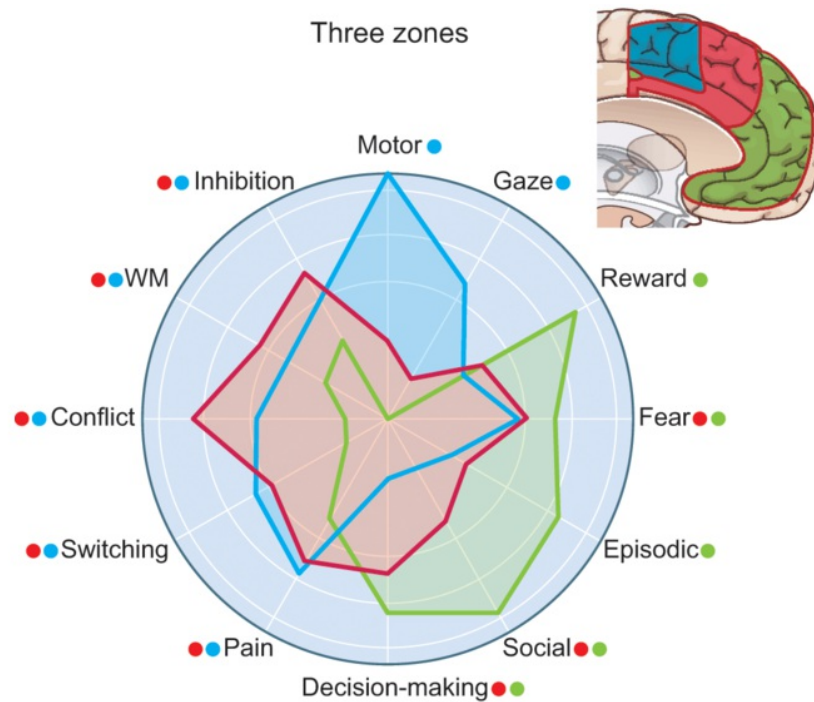


Figure 12.11 Cingulate cortex is involved in action, cognition, and emotion.

The cingulate lies directly above the corpus callosum. The anterior cingulate cortex has three main zones, a posterior section (shown in blue) that is associated with motoric functions, a middle zone associated with cognitive control (shown in red), and a rostral/ventral part (shown in green), implicated in emotion. The figure shows the degree to which each region is associated with particular processes. The closer the point is to the edge of the circle, the larger is the association with that function. Significant associations are indicated by a colored dot next to a function. Note that there is overlap in degree to which regions are associated with certain functions. For example, both the posterior and middle zones are approximately equally associated with pain.

(from de la Vega et al., [2016](#)).

The anterior cingulate is a region where emotion, cognition, and motor control interface. For example, one theoretical view is that the anterior cingulate cortex is involved in selecting motor actions, considering both the cost and effort entailed in those actions, and weighing how much reward has been gained by taking those actions previously (Rushworth et al., [2007](#)). Another viewpoint argues that the anterior

cingulate integrates affective signals with cognitive control to optimize actions in the face of uncertainty about an action's outcome (Shackman et al., [2011](#)).

Lesions of the anterior cingulate cortex can result in a variety of emotional sequelae, including apathy, inattention, emotional lability, and changes in personality and social interaction (Bush et al., [2000](#); Hadland et al., [2003](#)). In addition, the cingulate is also involved in pain (Tracey, [2005](#)), receiving input from subcortical structures that have neurons specialized to respond to noxious stimuli. Patients who received small cingulate lesions as a treatment for pain reported that the pain still existed but no longer bothered them as much (Cohen et al., [1999](#)). Some portions of the anterior cingulate appear to discriminate between the presence or absence of a painful stimulus but are not sensitive to pain intensity, whereas other portions appear to code the intensity of a painful stimulus (Büchel et al., [2002](#)).

Certain portions of the cingulate appear to have somewhat distinct roles. Traditionally, researchers made a distinction between the dorsal and rostral portions of the anterior cingulate cortex (Bush et al., [2000](#)). A more recent meta-analysis of functions associated with the anterior cingulate cortex suggest three main zones that are mainly involved, from posterior to anterior, in motor control, cognition, and emotion respectively (de la Vega et al., [2016](#)).

Several lines of evidence implicate the most anterior (rostral) region of the cingulate in emotional processing. First, this region is connected to many other emotion-related areas, including the amygdala, the hypothalamus, the insula, and the orbitofrontal cortex. Second, imaging studies suggest that the rostral region is especially activated by tasks that have an emotional component (Bush et al., [2000](#); Mohanty et al., [2007](#)). Activity in this region is also correlated with changes in the autonomic nervous system (e.g., Critchley et al., [2005](#); Matthews et al., [2004](#)), and has been linked to depression, as we will learn in [Chapter 14](#). In contrast, the dorsal portion of the cingulate has connections with lateral prefrontal cortex, parietal cortex, and motor areas. As we learned in [Chapter 11](#), this region is more involved in motoric and cognitive functions, especially executive control.

The dorsal and rostral subdivisions of the anterior cingulate may relate to one another in a reciprocal fashion at times. During cognitive task performance, activity often decreases in the rostral division while increasing in the dorsal division; during emotional conditions, activity often increases in the rostral division while decreasing in the dorsal division (Drevets and Raichle, [1998](#); Pessoa and Pereira, [2013](#)). These results suggest that there may be a reciprocal dynamic between emotion and cognition, with strong emotion functioning to shut down certain cognitive systems and vice versa. This notion seems intuitively appealing, as many of us have experienced for ourselves how an emotional state can interfere with paying attention to a nonemotional task. Conversely, many of us have also had occasion to “lose ourselves in our work” for the purpose of coping with an emotional stress or trauma.

These findings should not be taken, however, to suggest a strict and rigid dichotomy between the functions of these cingulate zones, as other evidence suggests that cognition and emotion are not so entirely separable (e.g., Etkin et al., [2011](#); Pessoa and Pereira, [2013](#); Shackman et al., [2011](#)). For example, a recent meta-analysis found that a particular region of the midcingulate cortex was activated by various manipulations of negative emotion, pain, and cognitive control (see [Figure 12.12](#); Shackman et al., [2011](#)), pointing to the cingulate’s role as an integrator of such information.



Figure 12.12 Overlapping areas of the cingulate cortex are activated by studies manipulating negative affect, pain, and cognitive control.

From Shackman et al., [2011](#).

EEG studies of the error-related negativity (ERN), which is generated by the cingulate cortex, also illustrate the complexity of teasing apart cognitive and emotional functions in the cingulate cortex. As discussed in [Chapter 11](#), the ERN is an electrical response that occurs when a person detects that he or she has made an error, or when a person receives negative feedback about performance. Influential theories describe the ERN as part of a system of cognitive control, a signal that indicates when outcomes are worse than expected (Holroyd and Coles, [2002](#)) or deviate from predictions (Alexander and Brown, [2011](#)). Because an error is usually an unpleasant outcome, we could think of the error signal as an emotional signal. Indeed, errors, and particularly those that produce larger ERN responses, are associated with increases in the defensive startle reflex, an emotional response (Hajcak and Foti, [2008](#)). In this sense, the fact that the ERN is generated by the cingulate cortex fits with the idea that the cingulate is involved in aspects of emotion. At the same time, an error signal also indicates the need for a change in attention or behavior, to avoid repeated mistakes.

In the end, it may be useless to try to pigeonhole divisions of the cingulate, or phenomena produced by the cingulate such as the ERN, as either strictly cognitive or strictly emotional. Instead, it is more useful to consider possible relationships between emotional signals and cognitive control. For example, signals of emotional salience can cue the need for cognitive control (Inzlicht et al., [2015](#)). Imagine you are driving down the road while not paying close attention, and start to accidentally drift toward an oncoming car. When you notice this looming danger, you will likely have a strong emotional reaction together with a redirection of your attention toward the task of driving as well as a motoric action of correcting your steering. Likewise, the sensation of pain, which activates the cingulate, is associated with a shift of attention toward the source of the pain and motivated efforts to take actions to relieve the pain. In these examples, signals of importance that are tagged by emotion (“there’s danger ahead!” or “there’s something that hurts!”) are communicated to systems that act to redirect attention and action.

The cingulate cortex clearly acts as a central hub linking emotion and cognitive

control so that salient information can influence attention and action. At the same time, other cortical brain regions are important in additional functions that integrate cognition and emotion in different ways. These functions include the influence of emotion on decision making, the regulation of emotion, and the communication of emotion through facial and vocal cues. We discuss each of these functions in turn in the next few sections.

Incorporating Emotion into Decision Making

Commonsense tells us that emotions affect decision making. When deciding how to spend your Saturday evening, your choices will be affected by memories of activities that you found to be either pleasant or unpleasant in the past. When choosing to vote for a political candidate, your decision may be influenced in part by the candidate's emotional appeals. Although the influence of emotion on decision making is sometimes considered troublesome because it is "irrational," some researchers argue that emotional signals are actually important cues that effectively guide us toward outcomes that benefit us and away from outcomes that harm us (e.g., Damasio, [1994](#)).

The brain region most implicated in integrating emotion and decision making is the [orbitofrontal cortex \(OFC\)](#). The OFC has been described as "among the least understood regions of the human brain" (Kringelbach, [2005](#), p. 691), partly because of differences in this region across species and notable variation in its anatomical structure from one person to the next. In addition, the OFC includes several different subareas whose functional distinctions are not yet clear. Here we use the term OFC to include both regions that directly overlie the eye orbits and areas that extend into the medial wall of the frontal lobes, an area that is sometimes referred to as the ventromedial prefrontal cortex (see [Figure 12.13](#)). Anatomical connections imply that the OFC is important in emotion, as this region is reciprocally interconnected with many other emotion-related structures such as the hypothalamus, amygdala, insula, and cingulate cortex. Although the overarching function of the OFC is still in dispute (see Stalnaker et

al., [2015](#)), current research implies that this region plays a role in attributing value to rewards and punishments and using that understanding to guide adaptive behavior (Padoa-Schioppa, [2011](#)).

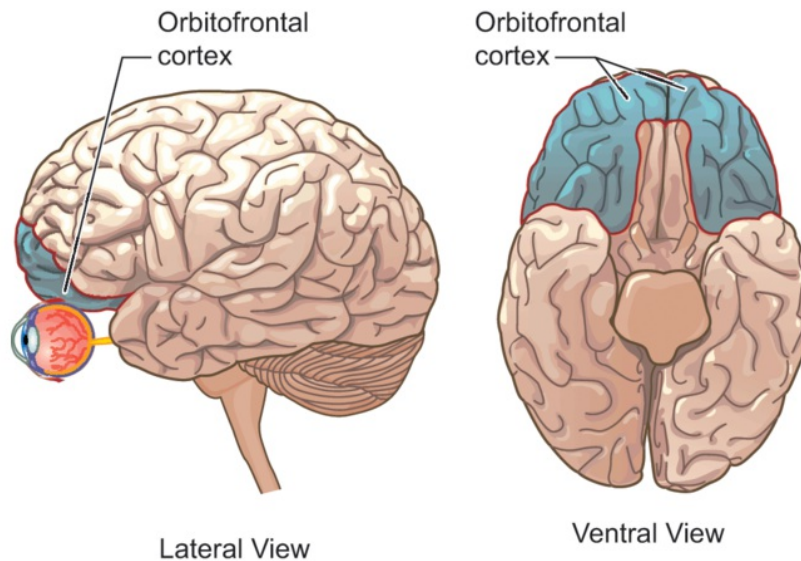


Figure 12.13 Location of orbitofrontal cortex.

The orbitofrontal cortex is so named because it lies directly above the eye sockets, or orbits. Sometimes the medial portion of the orbitofrontal cortex is referred to as ventromedial prefrontal cortex.

Case studies have shown that people with damage to the OFC exhibit disinhibited behaviors (e.g., grabbing things they want from others), socially inappropriate behaviors (e.g., blurting out tasteless remarks), and irresponsibility. They seem to have difficulty anticipating the consequences of their actions, they make poor decisions that result in negative outcomes, and they do not seem to learn from their mistakes (Bechara et al., [1994](#); Rolls et al., [1994](#)). These behaviors are especially remarkable because the patients show no deficits in intellectual ability as measured with standard IQ tests. Some researchers have even suggested that the OFC may provide the substrate for the development of moral behavior, comparing people with OFC damage to those with the psychiatric disorder of psychopathy, a failure of empathy often seen in violent criminals (Anderson and Kiehl, [2012](#)).

People with damage to the OFC perform especially poorly on tasks in which past losses and gains must be considered in order to make appropriate choices in the present. Such deficits have been empirically demonstrated using gambling tasks, in which the participant must choose a particular stimulus that results in either winning or losing money (Bechara et al., [2000](#); O'Doherty et al., [2001](#)). These tasks are designed so that people cannot simply associate one stimulus with one outcome; rather, the tasks are designed to work probabilistically, so that over time some choices tend to be better than others. In a gambling task, a person might win big by choosing a particular item, but continuing to choose that item over time results in a series of small losses, thus making this choice less profitable than an alternative choice. People with damage to the OFC tend to stick with the “big win” stimulus even though it leads to greater losses over time. This behavior resembles that of a child who cannot resist the impulse to eat a huge piece of cake despite knowing that later on it will lead to an upset stomach. As we discuss in more detail in [Chapter 14](#), similar impairments in decision making are also evident in substance abuse, in which people often make decisions on the basis of immediate gratification while ignoring the long-term consequences. In fact, difficulties in decision making in substance-dependent people are linked to atypical activation in orbitofrontal regions (Tanabe et al., [2013](#)).

The OFC is especially important for learning in situations that require the individual to respond to changing patterns of reward and punishment. Researchers often study this phenomenon by varying what is called the [reinforcement contingency](#), which simply refers to the degree to which a reward or punishment is associated with a particular stimulus or action. Single-cell recording studies in nonhuman primates show that neurons in the OFC respond to the rewarding value of taste, smell, and visual stimuli, and that some neurons respond only when the reinforcement contingencies change (Rolls, [1999](#)). People with OFC damage are impaired in the ability to change their behavior when the contingencies change. One example of such contingency change is referred to as [reversal learning](#). For example, let's say you were first rewarded for

pressing the left button in response to a red light and the right button in response to a green light. In reversal learning, you are now rewarded for pressing the left button for the green light and the right button for the red light. Reversal learning is deficient following OFC damage in humans and other primates (Roberts, [2006](#)). Neuroimaging studies also support the idea that the OFC tracks the changing reward value of a particular stimulus. For example, food becomes less rewarding as a person becomes satiated (full). Correspondingly, OFC activity decreases as the food becomes less desirable with satiation (Kringelbach et al., [2003](#)).

Some studies suggest that different subregions of the OFC respond to rewards versus punishments, an organization that may help the OFC to keep track of changing contingencies (Kringelbach, [2005](#)). According to this viewpoint, the lateral area of the OFC is activated following a punishing outcome in a gambling task, whereas the medial area is activated following a rewarding outcome (O'Doherty et al., [2001](#)). These two regions may act in a reciprocal manner: the medial region increases activation to reward and decreases activation to punishment, whereas the lateral orbitofrontal region exhibits the opposite pattern. Furthermore, the larger the reward or punishment delivered, the greater the brain activation. However, other research suggests that the value of a reward can best be determined by a distributed pattern of activity across orbitofrontal regions, as discerned from multivariate pattern analysis (Kahnt et al., [2010](#)). Regardless, the OFC allows us to represent the costs and benefits associated with any choice, leading to more informed and effective decision making.

The OFC is also crucial for evaluating the consequences of our choices. One of the ways that we think about the consequences of our own decision making is to consider what might have happened if we had made a different choice. Would I have been happier if I had bought the Honda rather than the Chevy? When we discover that we made the “wrong” choice, we often feel regret. Interestingly, patients with OFC damage do not appear to feel regret (Camille et al., [2004](#)).

Neuroimaging research with neurologically intact people has also found that the OFC is active in situations of regret. For example, the OFC becomes activated when

participants learn that a choice they rejected would have led to a greater benefit ([Figure 12.14](#); Coricelli et al., [2005](#)). OFC activity is especially tied to situations in which participants felt agency (responsibility) for the choice, rather than instances in which the undesired outcome was simply a matter of chance. When participants in this study were faced with similar choices again, the OFC became reactivated in anticipation of the choice, presumably as participants reconsidered the regrettable consequences of their previous actions.

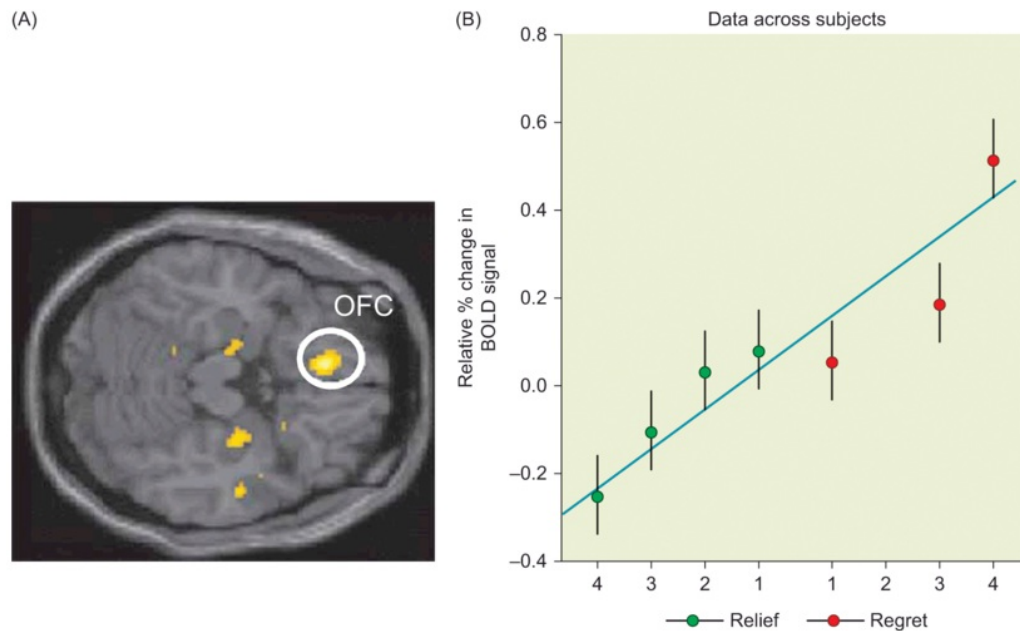


Figure 12.14 Orbitofrontal cortex responds to degrees of regret in a decision-making task.

Levels of regret (1–4) are defined by the discrepancy between what a participant earned from a particular choice and what she might have earned had she made a different choice. For example, level 4 of regret represents a condition in which the participant discovered that she lost 200 points when she could have gained 200 points if she had picked the other option. Level 1 of regret represents a condition in which the participant lost 50 points but could have earned 50 points. Levels of relief represent conditions in which the participant learned that she made the right choice, such as by earning 200 points when she could have lost 200 points (level 4 of relief) or by earning 50 points when she could have lost 50 points (level 1 of relief). Activity in the orbitofrontal cortex tracks the value of the actual choice relative to the value of the path not taken.

Source: Adapted by permission from Macmillan Publishers, LTD: Coricelli, G., Critchley, H. D., Joffily, M., O'Doherty, J. P., Sirigu, A., & Dolan, R. J. (2005).

Regret and its avoidance: A neuroimaging study of choice behavior. *Nature Neuroscience*, 8, 1255–1262. Figure 4a.

While you may think of regret as a uniquely human feeling, even rodents appear to think back on missed opportunities. One clever study demonstrated that OFC neurons in

rats may replay a pattern of activity associated with a missed chance (Steiner and Redish, [2014](#)). In the study, rats had to choose among four zones associated with different treats, a scenario dubbed “Restaurant Row.” Once in a particular zone, the rat would hear a tone indicating the wait time for receiving the treat in that zone. The rat had to decide whether to wait or whether to move on, taking a chance on a shorter wait in the next zone. (You may have had similar experiences making decisions between restaurants with long waiting times.) In some situations, the gamble wouldn’t pay off, and the rat would find that it had to wait even longer in the next zone. In such conditions, rats looked back toward the zone they had just opted against, and neurons in the OFC mirrored the pattern associated with the passed-over reward. Of course, it is hard to know whether the rat was really pining for what might have been. Nevertheless, this evidence from the level of individual neurons converges well with human clinical and neuroimaging studies indicating that cells in the OFC code for the value of choices, including the paths not taken.

Regulating Emotion

An important aspect of emotion is being able to control it. If you’ve ever cheered yourself up after a bad day, suppressed your anger after a friend made an unfair or callous remark, or practiced meditation to help relieve stress, you’ve engaged in some form of emotion regulation. [Emotion regulation](#) generally refers to attempts to manage the emotions that one experiences, so that they are socially appropriate and do not spiral out of control. Emotion regulation may be disrupted in certain clinical conditions, such as mood disorders. Although many strategies for emotion regulation are conscious, voluntary efforts, emotion regulation may take place at an unconscious level as well.

While emotion regulation has been defined rather broadly, some researchers have proposed frameworks to organize thinking about different aspects of emotion regulation. [Figure 12.15](#) depicts a variety of self-regulatory steps potentially occurring at different timepoints in relation to an emotional event (Gross, [1998](#), [2013](#)). To illustrate, imagine

that you feel very anxious, even panicky or phobic, about giving class presentations. One strategy you might take is situation selection: perhaps you might try to avoid class presentations by choosing only classes that don't require any presentation. Alternatively, you might try situation modification: you might try to schedule a required presentation for a time in the semester when you don't anticipate a lot of other stressors, or you might see if you can work with a partner to make the presentation less stressful. Using the strategy of attentional deployment, you might try to distract yourself by thinking of other things during the lead-up to the presentation, or while giving the presentation, you might direct your attention to the smiling face of your friend in the audience. Cognitive reappraisal is a strategy of rethinking the meaning of the event; for example, you might try to think, "giving this presentation is an important learning experience for me that will help me later in my career," or "other students are not judging me as much as I fear, because they all understand that almost everyone gets nervous for presentations even if they don't show it." Finally, response modulation refers to modifying the outward expression of an emotion, for example attempting to smile calmly even when nervous, or trying to steady one's shaking hands. All of these steps (and maybe more) reflect ways that we can try to modify our own experienced and expressed emotion.

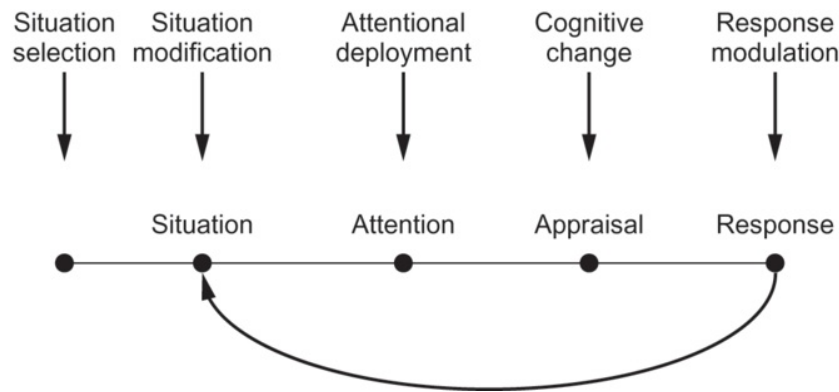


Figure 12.15 Processes involved in emotion regulation.

For any emotional event, there are numerous steps in which emotion regulation could be applied, ranging from selecting the situation to modulating the emotion expressed as a result of the situation.

(from Gross, [2013](#))

Most cognitive neuroscience research on emotion regulation has been conducted on cognitive reappraisal, and, to a lesser extent, attentional deployment and response modulation (Ochsner et al., [2012](#)). Numerous studies have shown that cognitive reappraisal can reduce the brain's responsiveness to emotional information. For example, participants might see a picture of a snarling dog with teeth bared. Instead of thinking about how frightening it would be to run into such an animal, participants would be instructed to try to view the picture in a more positive way, such as by imagining that the dog was protecting them from an intruder.

Results from ERP studies support the conclusion that engaging in cognitive reappraisal reduces neural markers of attention to emotional information. For example, negative pictures usually produce a significantly larger P300 response in the ERP waveform, compared to neutral pictures, presumably because the P300 reflects allocation of attention, which is greater for emotional than neutral pictures. However, engaging in reappraisal lessened this effect, implying that attention was not as strongly captured by negative images when participants were engaging in cognitive reappraisal (Hajcak and Nieuwenhuis, [2006](#); see also Foti and Hajcak, [2008](#)). The P300 response

to positive pictures can also be lessened by reappraisal strategies, paralleling the effects shown with negative pictures (Krompinger et al., [2008](#)).

Neuroimaging studies can help to distinguish between brain regions that are responsible for exerting top-down control (the “source” of emotion regulation) and those whose activity is being modulated (the “target” of emotion regulation; see Kalisch et al., [2005](#)). For example, imagine a situation in which you are about to experience a painful medical procedure. You may try to reduce your anxiety by mentally detaching yourself (e.g., by imagining that you are lying on a cozy blanket in a lovely field of flowers with warm sunshine beaming down on you). Such strategies tend to lessen perceived pain. What brain regions are involved in generating the “detachment” experience (the source of emotional control), and how do those brain regions affect the regions that would normally code for pain (the target of control)?

Generally, when people voluntarily try to control their emotions, activity increases in frontal lobe regions involved in cognitive control (presumably the source of regulation) and decreases in subcortical regions that would normally process that emotion (presumably the target of regulation; Buhle et al., [2014](#)). For example, one study showed sexually provocative pictures to men and instructed them to suppress their sexual arousal responses to the pictures. In this suppression condition, brain activity increased in the right superior frontal gyrus and decreased in the hypothalamus and amygdala, compared to a simple viewing condition (Beauregard et al., [2001](#)) (see [Figure 12.16](#)). Likewise, when participants were instructed to reevaluate disturbing pictures in a way that would reduce their negative feelings, frontal lobe activity increased and amygdala activity decreased (Ochsner et al., [2002](#); see also Denny et al., [2015](#)). Other investigators found that when participants were required to suppress emotional memories, the right inferior and middle frontal gyrus regions became more active, and hippocampal and amygdala regions less active (Depue et al., [2007](#)).

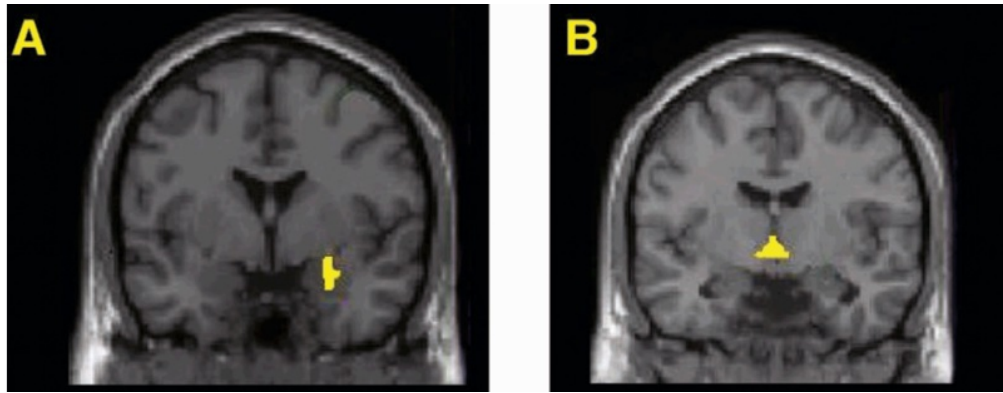


Figure 12.16 Influence of emotion regulation on subcortical regions.

The amygdala (panel A) and hypothalamus (panel B) were activated when men viewed sexually provocative pictures. Those same regions showed no activity when the men were asked to inhibit their arousal responses.

Source: Figures 1a and 1c from Beauregard, M., Levesque, J., and Bourgoin, P. (2001). Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience*, 21, RC165 (1–6). Permission conveyed through Copyright Clearance Center, Inc.

Stimulation studies can go beyond neuroimaging studies in addressing the causal role of specific brain regions in emotion regulation. Because neuroimaging studies can only tell us how brain activity is correlated with different cognitive states, they can't definitively indicate whether a particular region, such as a region of frontal cortex, is truly a cause of emotion regulation, as opposed to a side effect of that regulation. To address this limitation, one study used tDCS to stimulate dorsolateral prefrontal cortex during cognitive reappraisal or free-viewing conditions (Feeser et al., 2014). The stimulation improved the effectiveness of cognitive reappraisal strategies in modifying peripheral measures of emotional arousal, such as skin conductance. Thus, increasing dorsolateral prefrontal activity had a cause-and-effect impact on emotion regulation.

While most research has focused on cognitive strategies that alter the meaning of the event in some way (i.e., cognitive reappraisal), other research has investigated altering attention as a means of regulating emotion. For example, when people are anxious, they tend to focus their attention on potentially threatening information. However, people can

be trained through implicit measures (without awareness) to redirect attention away from threatening information, and such training reduces anxiety (see Bar-Haim, [2010](#), for review). Neuroimaging data suggest that control regions in the frontal lobe are implicated in such attentional bias training as well (Browning et al., [2010](#)).

Not surprisingly, regulating emotion is taxing on mental resources. Perhaps because strategies such as cognitive appraisal draw upon the same frontal lobe control systems that we use for executive functions, engaging in challenging emotion regulation activities seems to have an immediate effect of reducing performance on executive function tasks such as Stroop conflict resolution (e.g., Inzlicht and Gutsell, [2007](#)). Unfortunately, stress itself also taxes executive functions due to the negative impact of stress on prefrontal cortex functioning (e.g., Arnsten, [2015](#)). This may explain why in stressful real-life circumstances, we are often unsuccessful in using cognitive reappraisal to modify our emotions. Indeed, one study found that after experiencing an acute stressor in the lab (sticking one's hands in a bucket of ice water, a manipulation known as the cold pressor test), participants were less effective in using cognitive reappraisal to reduce fear conditioning, compared to participants in a control condition, who used cognitive reappraisal effectively (Raio et al., [2013](#)). Such research reminds us of the limits of emotion regulation strategies in various contexts. Though much remains to be learned about emotion regulation, in general these studies so far tell us that when people adopt strategies of emotional control, they can change how their brains respond to emotional situations.

Communicating and Interpreting Emotional Signals

Our emotions are not just felt internally; they are also conveyed to other people. Although we tend to think of language as the dominant means of communication in our species, nonverbal signals of emotion communicate important information among members of a social group. If you meet a friend and notice that her facial expression is angry, you will interact with her differently than if her face bears a happy expression. Likewise, a phrase such as "Susan and Bill have just eloped" can convey very different

sorts of information depending on whether it is spoken in an excited, surprised, sad, or angry tone of voice. In the next two sections, we consider the neural systems involved in both perceiving and producing expressions of emotion.

Facial Expressions

The ability to produce and recognize facial expressions of emotion is nearly universal. Dating back more than 50 years, evidence from cross-cultural studies has been used to argue that similar facial expressions are used across a wide range of cultures to convey basic emotions such as happiness, sadness, anger, fear, surprise, and disgust (see [Figure 12.17](#); e.g., Ekman et al., [1969](#); Elfenbein and Ambady, [2002](#); for critique, see Gendron et al., [2014](#)). Although there are some differences across cultures in the exact way that expressions are formed and the social contexts in which they are considered appropriate (e.g., Marsh et al., [2003](#); Matsumoto et al., [2005](#)), the strong similarity of basic expressions across cultures implies that these expressions are rooted in our species' common biological heritage, as recognized by Charles Darwin more than a century ago (Darwin, [1873](#)). So, what do we know about the neural mechanisms that recognize and produce facial expressions?



Figure 12.17 Facial expressions that are universally recognized.

From left to right, the top row shows expressions of happiness, anger, and surprise, and the bottom row shows disgust, sadness, and fear.

Courtesy of Paul Ekman.

One of the most reliable findings in cognitive neuroscience is the right-hemisphere specialization for both recognizing and producing facial expressions of emotion. Right-hemisphere damage, particularly to temporal and parietal regions of the brain, disrupts the ability to recognize faces much more than does comparable left-hemisphere damage (Borod et al., 1998). The most severe impairments in emotion recognition have been attributed to damage of the right parietal cortex. However, right anterior temporal lobectomy, a common treatment for medically intractable epilepsy, has also been shown to cause impairments in processing emotional information, especially negative emotion in faces (see Adolphs et al., [2001](#)).

One important question is whether the perception of emotional expressions relies upon the same neural mechanisms as the perception of facial identity. As you remember from [Chapter 6](#), patients with prosopagnosia (due to occipitotemporal lobe damage) are unable to recognize the identities of individuals by their faces, but they are sometimes able to recognize emotional expressions (e.g., Tranel et al., [1988](#)). Conversely, some

patients have trouble recognizing emotional expressions, but can recognize individuals' identities from their faces (e.g., Young et al., [1993](#)). This double dissociation implies that recognition of facial expression and recognition of facial identity rely upon partly separable mechanisms.

Of course, both expression and identity recognition are likely to involve some similar steps in visual processing, such as constructing a coherent visual representation of the face structure. For this reason, it is not surprising that viewing emotionally expressive faces leads to activation in the fusiform gyrus of the right hemisphere, the region that is known to be differentially engaged in processing faces compared to other visual objects (e.g., Blair et al., [1999](#); Kawasaki et al., [2012](#)). However, the double dissociation tells us that beyond the stage of perceiving the visual image as a face, somewhat different brain regions are implicated in linking that face image with emotional information versus identification information.

Although there is overlap among brain systems that process the six main facial expressions – fear, disgust, anger, surprise, happiness, and sadness – it appears that not all emotional expressions are treated equally by the brain (Hennenlotter and Schroeder, [2006](#)). Fear is the expression for which there is the most evidence of a distinct neural substrate. For example, patients with damage to the amygdala are impaired in recognizing facial expressions, but these deficits seem to be most pronounced for fearful faces (Adolphs et al., [1999](#); Calder et al., [1996](#)).

Some of the difficulty in recognizing facial expression may arise from the fact that amygdala-damaged patients do not seem to direct their eyes to the most emotionally informative parts of the face, such as the eyes (see [Figure 12.18](#); Adolphs et al., [2005](#)). In fact, neuroimaging evidence shows that in neurologically intact people, the amygdala is responsive to specific facial features that indicate fear, such as enlarged whites of the eyes (Whalen et al., [2004](#)). Thus, in amygdala-damaged patients, an inability to detect these specific cues may lead to the deficit in recognizing fear expressions.



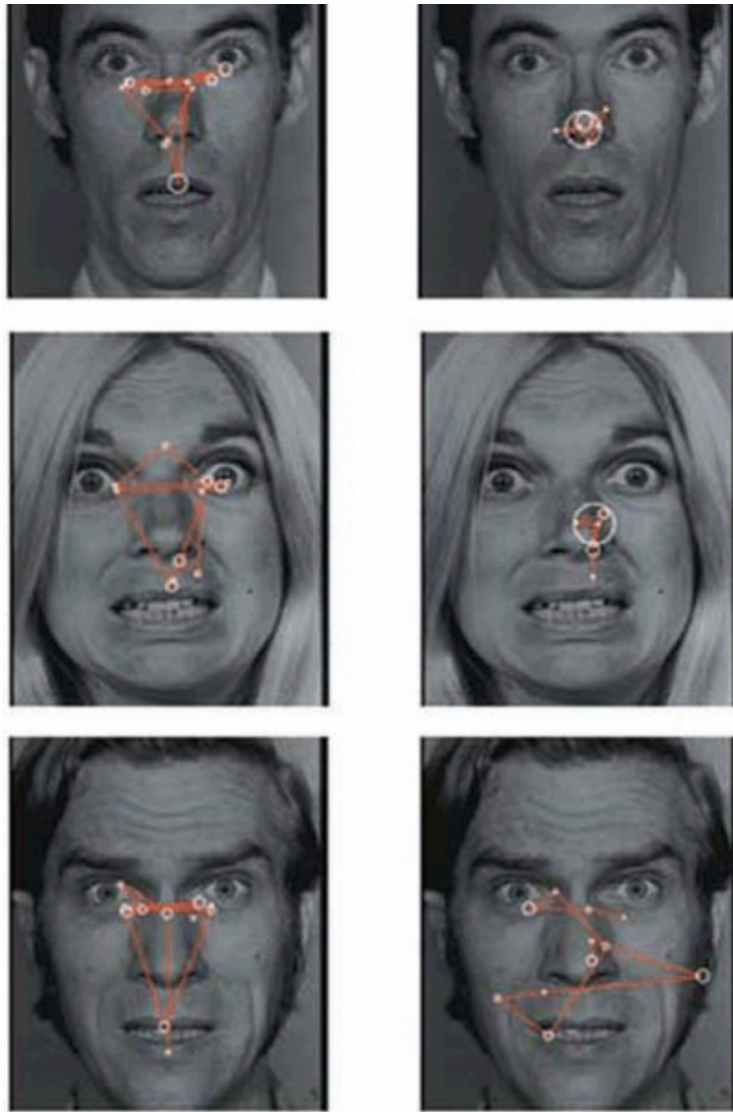


Figure 12.18 Patients with amygdala damage look at faces differently than neurologically intact individuals do.

The column on the left shows the eye-movement patterns of a normal participant; the column on the right shows the patterns of an amygdala-damaged patient when viewing fearful faces. Notice that the gaze of the normal participant is centered on examining the eyes and mouth, whereas the individual with amygdala damage tends to focus on the nose.

Adapted by permission from Macmillan Publishers, LTD: Figure 2 in Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., and Damasio, A. R. (2005).

A mechanism for impaired fear recognition after amygdala damage. *Nature*, 433, 68–72.

Of course, the amygdala does not recognize facial expressions on its own, but rather it interacts with face processing regions in inferotemporal cortex. A study combining fMRI with lesion techniques in monkeys illustrates this point (Hadj-Bouziane et al., [2012](#)). In monkeys without lesions, viewing expressive faces (threat and fear expressions) led to greater activity than neutral faces in both the amygdala and inferotemporal cortex. However, in monkeys with lesions to the amygdala, the inferotemporal cortex did not show an enhanced response for emotional versus nonemotional faces, even though it did still show an enhanced response for faces compared to nonface objects. Thus, input from the amygdala appears to be critical in driving the inferotemporal region's heightened response to the emotionality of the face.

The studies just discussed have focused on perceiving facial expressions; but what about the ability to impart emotion in a facial expression? Several muscles in the face seem to have evolved for the sole purpose of forming emotional expressions (see [Figure 12.19](#)). Facial muscles move when they receive input from cranial nerves that are controlled by the brain's various motor systems (see [Chapter 4](#)). There are at least two systems for control of facial expressions: a system centered in the basal ganglia that controls spontaneous or automatic facial expressions, and a system centered in the motor cortex that controls voluntary facial expressions. Thus, a patient with damage to the basal ganglia (such as a patient with Parkinson's disease) may not make any facial expressions in spontaneous conversation, contributing to a mask-like appearance, but he or she may make posed facial expressions if explicitly instructed to do so or with voluntary effort.

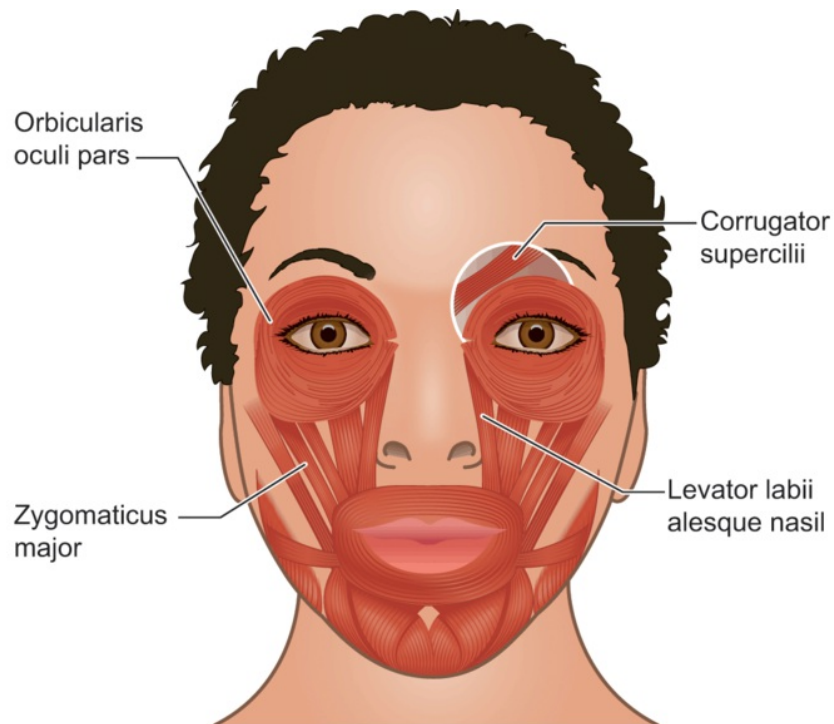


Figure 12.19 Muscles of the face that are used to make facial expressions.

The corrugator muscle is used to furrow the brow, as in anger or fear; the orbicularis and zygomaticus muscles are used in smiling, and the levator labii muscles are used to wrinkle the nose in disgust.

(from Niedenthal, [2007](#))

Just like the perception of facial expressions, the production of facial expressions appears to be more under the control of the right than the left hemisphere. In one research approach, the facial expressions of patients with unilateral brain damage are photographed or videotaped while the patients are talking, watching emotional films, or doing other tasks. The photographs or videotapes are then rated, either subjectively by judges or by using coding schemes to identify the muscle movements in the face. Typically, patients with right-hemisphere damage are found to be less expressive than those with left-hemisphere damage (e.g., Montreys and Borod, [1998](#)).

In another approach, typically used with neurologically intact individuals, the emotional expression appearing on the left side of the face is compared with that appearing on the right. Often, we can observe facial asymmetries merely by looking at a

face, as shown in [Figure 12.20](#). However, one way to quantitatively evaluate facial asymmetry is to cut a picture of a person's face in half and to splice each half-face together with its mirror-image to create a composite. The result is two chimeras, one consisting of two left half-faces and the other of two right half-faces. When this is done, we can instantly see large differences in the appearance of the two sides of the face (see [Figure 12.21](#)). People typically rate left-face composites as more expressive than right-face composites (Sackeim et al., [1978](#)). Moreover, high-speed videography approaches have quantified asymmetries in the initiation of facial expressions, finding that spontaneous expressions tend to start on the left side of the face, implying right-hemisphere dominance (Ross and Pulusu, [2013](#)). Nonhuman primates, like macaque monkeys and chimpanzees, also exhibit more dramatic expressions on the left side of the face (Fernandez-Carriba et al., [2002](#); Hauser, [1993](#); Wallez and Vaclair, [2012](#)).



Figure 12.20 Striking asymmetries in facial expression of emotion.

Although we think of people's faces as symmetrical, asymmetries can be seen. Note the asymmetrical expressions on some well-known faces: (A) the Mona Lisa, (B) Marilyn Monroe, (C) Elvis Presley, and (D) John Wayne.

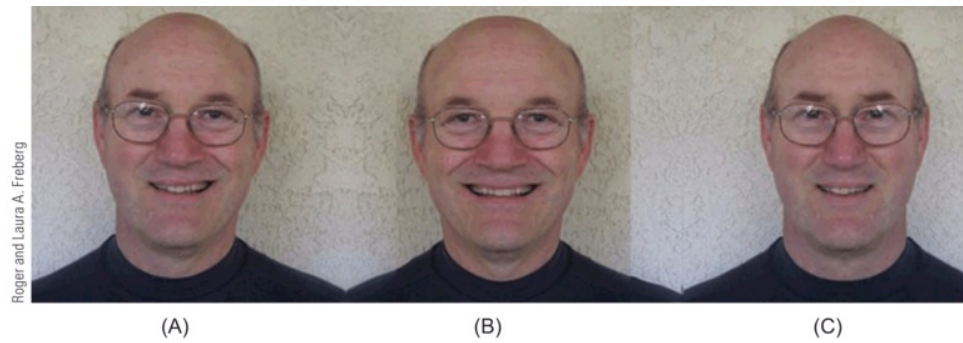


Figure 12.21 One method of demonstrating asymmetry of emotional facial expression.

An original photograph of the face, shown here in (A), is bisected. Then, each half-face is spliced together with its mirror-image to create a composite. Note the difference between the two composites depicted in (B) and (C). Which one looks more emotionally intense to you? Usually, individuals choose the composite composed of two left half-faces, depicted in (B), as more intense than the composite composed of two right half-faces, depicted in (C). This result suggests that the right hemisphere, which controls the lower left half of the face, has a larger role in producing facial emotional expression.

Courtesy of Roger and Laura A. Freberg.

If you've carefully followed our discussion of hemispheric differences in perception and expression of emotion in the face, you may have noticed an odd paradox. Remember that, because of right-hemisphere specialization for emotional expression and perception, emotion is most strongly expressed on the left side of a poser's face (due to right-hemisphere specialization in the poser), and that people are best at understanding emotional expressions seen in the left visual field or left side of space (due to right-hemisphere specialization in the viewer). This means that for two people directly facing each other in a communication context, the most expressive side of the poser's face will fall into the least sensitive half field of the viewer! (See [Figure 12.22](#) if you are having some left-right confusion.) This doesn't seem to be optimally adaptive for the purpose of communication.

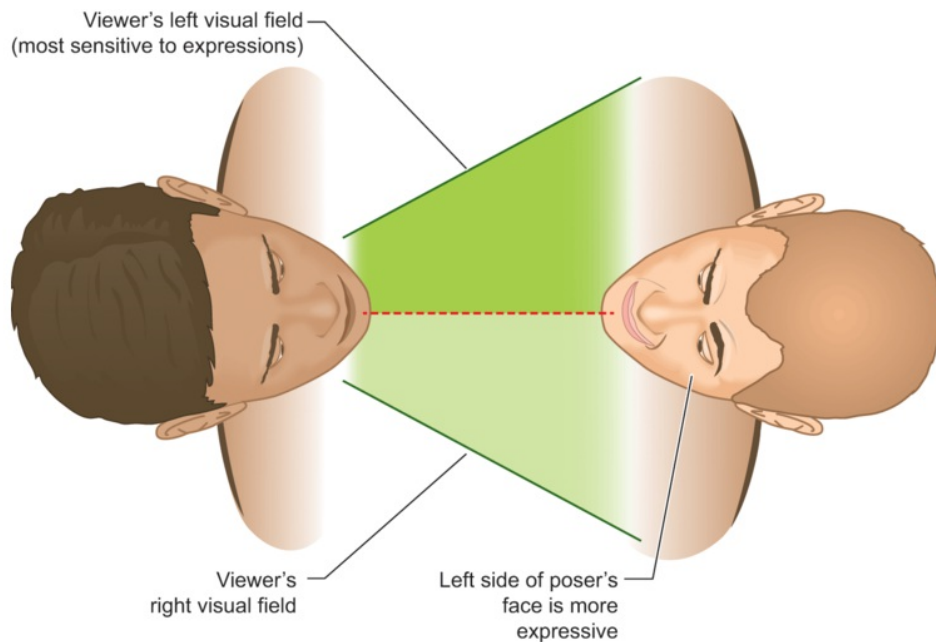


Figure 12.22 Expressive asymmetry meets perceptual asymmetry.

When two participants interact in face-to-face conversation, the more expressive left side of one person's face is projected onto the less-sensitive right visual field of the other person. This illustrates the paradoxical outcome when both participants have right-hemisphere specialization for emotional expression and perception. However, people tend to adapt to this phenomenon in real life by turning the head to show more of the left side of the face.

Interestingly, some research has shown that when people wish to communicate emotional information, they turn slightly to show more of the left side of the face. Analyses of portraits throughout history reflect a bias toward showing more of the left portion of the face, unless the portraits were made of scientists, who presumably put less emphasis on emotional expressivity (McManus and Humphrey, [1973](#); Nicholls et al., [1999](#)). When participants are asked to pose for a photograph in which they are encouraged to show their emotions, they are more likely to show the left cheek than if asked to pose for an “impassive” photo (Nicholls et al., [1999](#)). This turning bias in portraiture illustrates how cerebral asymmetries for emotion can subtly manifest themselves in everyday life.

Prosody

Prosody refers to the tone of voice in which a phrase is uttered. Monrad-Krohn (1947) first coined the term to describe vocal cues such as pitch or frequency, stress, intensity, and timing. Two types of prosody have been described. **Propositional prosody** communicates lexical or semantic information – for example, “What’s that in the road ahead?” versus “What’s that in the road, a head?” **Affective prosody** communicates the emotional context or tone of an utterance – for example, “My mother is coming to dinner” could be stated in a way that expresses either elation or dismay. Within the general category of affective prosody, researchers have distinguished between prosody that conveys the emotional state of the speaker (called emotional prosody, including happy, sad, and angry tone of voice) and prosody that conveys an attitude toward a person or object (called attitudinal prosody, including sarcasm and superiority) (Mitchell and Ross, 2013). Although prosody has been less well studied than facial expression as a means of conveying emotion, there is no question that prosodic cues are important in social interaction. For example, when you talk with a friend on the phone, you have no information about his facial expression, but you can use affective prosodic cues to deduce his emotional state or intent.

Deficits in comprehension of prosody as a result of brain damage are referred to as **aprosodia**. Clinical studies indicate that patients with right-hemisphere lesions are significantly impaired in comprehending prosody, compared to patients with left-hemisphere lesions (e.g., Ross, 2013). In particular, aprosodia tends to be associated with damage to the region around the Sylvian fissure on the right side of the brain. This localization makes logical sense, complementing the role played by left-hemisphere Sylvian regions, which are more heavily involved in the auditory processing of language and language comprehension.

Nonetheless, there is some debate in the literature about the lateralization of prosody comprehension, because left-hemisphere damage can also lead to difficulties in interpreting prosody (Pell, 2006; van Lancker and Sidtis, 1992). Some researchers have

suggested that the right hemisphere is important for comprehending affective prosody (e.g., determining the emotional state of a speaker) and the left hemisphere for comprehending propositional prosody (e.g., distinguishing questions from statements based on tone of voice) (Walker et al., [2002](#)). Other researchers have argued that left-hemisphere contributions to prosody may involve incorporating prosodic cues, which were initially decoded by the right hemisphere, into the overall semantic understanding of language that is dominated by the left hemisphere (Pell, [2006](#)).

Neuroimaging studies have also implicated the right hemisphere in perceiving affective prosody. For example, one study compared a condition in which participants had to distinguish the emotional tone of a voice (e.g., angry versus happy) to another condition in which they had to distinguish different phonemes within words (e.g., power versus tower) (Buchanan et al., [2000](#)). Both tasks activated both hemispheres, but the activation was greater in right inferior prefrontal cortex for the emotion task and in the left inferior prefrontal cortex for the phoneme task. This study also found significant activity in the right auditory cortex for the emotional condition. More recently, a meta-analysis of more than 29 neuroimaging studies found evidence of reliable activation of right auditory cortex, as well as bilateral lateral inferior frontal cortex, during tasks of affective prosody (Belyk and Brown, [2014](#)).

The production of prosody is also heavily dependent on the right hemisphere (Ross, [2013](#)). For example, some studies have presented brain-damaged patients with neutral sentences and asked them to repeat the sentence in different tones of voice (e.g., happy, sad, angry, or indifferent). Typically, individuals with right-hemisphere damage speak in more of a monotone (e.g., Tucker et al., [1977](#)). As you might expect, deficits in producing prosody tend to be associated more with anterior rather than posterior regions within the right hemisphere (see [Figure 12.23](#); Ross and Monnot, [2008](#)). Other work with clinical populations has focused on examining whether more specific components of the production of prosody, such as the basic frequency at which an utterance is made (known as the fundamental frequency), intensity, and timing parameters, may be differentially lateralized. Deficits in producing fundamental

frequency may be associated with right-hemisphere damage, and deficits in producing timing parameters may be associated with left-hemisphere damage (Pell, [1999](#)).

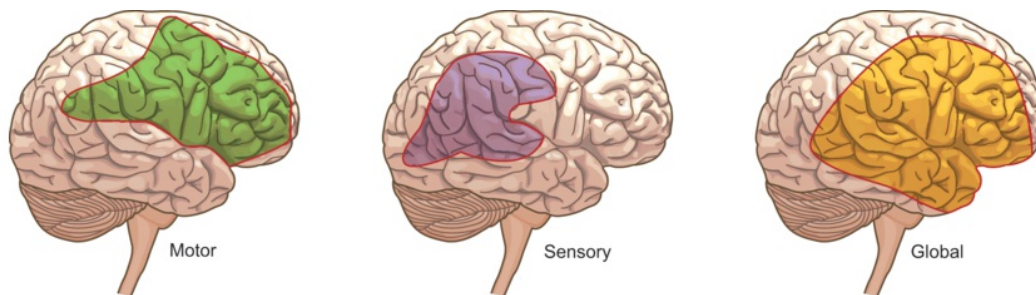


Figure 12.23 Areas of the right hemisphere that, when damaged, lead to difficulties in perceiving or producing emotional prosody.

The nomenclature used to name these disorders is parallel to that used for aphasia (see [Chapter 8](#)). Frontal lobe damage is associated with poor production but intact comprehension (motor aprosodia), temporoparietal damage is associated with intact production but poor comprehension (sensory aprosodia), and widespread damage to the right hemisphere is associated with deficits in both spontaneous production and comprehension of prosody (global aprosodia).

(from Ross, [2006](#))

Neuroimaging studies of prosodic production have emphasized the involvement of both subcortical motor regions, namely, the basal ganglia, and lateralized right-hemisphere cortical regions. For example, in one study, participants were cued about which prosodic tone to use for an upcoming sentence (Pichon and Kell, 2013). Participants heard an auditory word (e.g., the word fearful, happy, sad, angry, or neutral) and were instructed to read an upcoming visually presented sentence in that tone of voice. By introducing a delay between the prosodic cue and the sentence to-be-read, the researchers could examine the brain areas activated by the general intent to produce a particular emotional tone, separate from the process of preparing to speak a particular sentence. The basal ganglia (dorsal and ventral striatum) were activated bilaterally by the instruction to produce emotional versus neutral tone of voice for the upcoming sentence. When the sentence was actually uttered (the speech execution

phase), emotionally intoned sentences were associated with greater activity (compared to neutral sentences) bilaterally in inferior frontal regions and asymmetrically in right superior temporal lobe. These results indicate that prosody production cannot be attributed solely to right-lateralized cortical regions, but rather involves basal ganglia in both hemispheres during the preparation phase and right lateralization primarily in the execution phase of prosody production.

In sum, the communication of emotion requires both the ability to perceive another person's emotional meaning, whether conveyed through the face or the voice, and the ability to produce one's own emotional communications, again whether through the face or voice. In this way, emotional communication is like language, which also has receptive and expressive (production) components and is used to impart information to others. Unlike many aspects of language, however, emotional communication is more dependent on systems of the right hemisphere rather than the left hemisphere. In addition, cortical processing regions for perception and motor control interact with subcortical systems, such as the amygdala and basal ganglia, to enable the full repertoire of emotional communication.

Models of Emotional Experience

Thus far we have considered the role of various cortical brain regions in representing bodily states of emotion, integrating emotion and cognition, regulating emotion, and communicating emotion through facial and vocal expressions. A final emotional function is the experiential aspect of emotion. Scientific questions about how we “feel inside,” that is, what our internal emotional states are like, are distinct from questions about how we process information in the world that has emotional significance or how we impart communicative signals about emotion to others.

Although we can experience a wide range of emotions – happiness, sadness, fear, rage, etc. – psychologists and neuroscientists generally agree that there is not a one-to-one mapping between brain regions and emotional experiences. That is, there is no

“happy” brain region nor a “sad” brain region. Yet, clearly the emotional experiences of happiness and sadness must be somehow distinct in the brain because they are distinct in our behavior and experience.

Researchers have taken two basic approaches to considering the neural basis of felt emotional experience. Some models assume that there are fundamental underlying dimensions of emotional experience that can account for a wide range of emotions. These models argue that basic dimensions of emotion (such as pleasantness–unpleasantness, or low-arousal–high-arousal) map onto specific brain systems. A different approach assumes that emotional experiences are not dimensional, but rather each unique emotion derives from distributed activation across a large set of brain regions. According to this idea, there may be considerable overlap in the distributed pattern of brain activity associated with different unique emotions; there is no simple one-to-one mapping between an emotional experience or dimension and a particular brain region.

One influential dimensional model assumes that the basic dimensions of emotional experience are best described in terms of approach and withdrawal motivations. For example, happy states involve a tendency to approach and engage with the world, whereas sad states involve a tendency to withdraw from it. Another type of model argues that the basic dimensions of emotion are valence (positive versus negative emotions) and arousal (low versus high emotional intensity). As we discuss in this section, each of these dimensional models has been related to activity in certain cortical regions.

According to the [approach-withdrawal model](#), approach and withdrawal are the most basic and rudimentary actions that organisms take in responding adaptively to the environment (for reviews, see Davidson, [2004](#); Sutton, [2002](#)). As emotions evolved, they became associated with already established approach or withdrawal action systems. Proponents of this model propose that the left frontal region houses a system involved in approach behaviors. Therefore, increased activity of the left frontal area is associated with emotions that tend to be accompanied by approach behaviors, including

most positive emotions. In contrast, the right frontal region is posited to house a system involved in withdrawal behaviors. Increased activity of the right frontal area is associated with emotions– such as fear, disgust, and depression– that are accompanied by withdrawal behaviors.

Much of the evidence supporting the approach-withdrawal model is based on EEG measures of activity in right or left frontal regions, which vary from person to person depending on the individual's typical outlook or disposition. For example, EEG measures reveal that people differ in the degree to which they show more right versus left prefrontal activity during a resting baseline condition (Coan and Allen, [2004](#)). These asymmetries predict a person's disposition, with more left frontal activity associated with a more optimistic or positive outlook and more right frontal activity associated with a greater reactivity to negative stimuli. These patterns were replicated in 10-month-old infants, who were more likely to cry when separated from their mothers if they had more right than left prefrontal activation (Davidson and Fox, [1989](#); see also Buss et al., [2003](#)). Similar patterns of asymmetry exist in rhesus monkeys, who show higher levels of stress hormones if they have more right than left prefrontal activation (Kalin et al., [1998](#), [2000](#)). Such asymmetries are also associated with transient changes in mood. Increased left frontal activity is observed when people view happy film clips (Davidson et al., [1990](#)) or when infants receive sweet-tasting sugar water (Fox and Davidson, [1986](#)).

A similar relationship between hemisphere of activation and mood state has been observed in clinical populations with affective disorders. For example, during a resting condition, people with depression showed more activity in the right prefrontal region than in the left, whereas nondepressed people showed the opposite pattern (Schaffer et al., [1983](#); Shankman et al., [2007](#); Thibodeau et al., [2006](#)). Other studies have found that experiencing psychosocial adversity during development, such as maternal depression, childhood maltreatment, or institutionalization, is associated with a rightward shift in EEG asymmetry over the frontal lobes (Peltola et al., [2014](#)). In fact, greater right than

left EEG activity in the frontal lobe regions may reflect a risk factor for depression, as discussed further in [Chapter 14](#).

Recent studies have integrated the approach-withdrawal model with neurotransmitter systems that are known to play a role in motivated behavior. For example, the neurotransmitter dopamine is important in both motor control and reward-related behavior, so it follows that dopamine activity may be especially relevant to the approach dimension of the approach-withdrawal model. One study examined left-right asymmetry of dopamine receptor binding in people who differed in whether they tended to show better learning from rewards or from punishments (Tomer et al., [2014](#)). Consistent with the approach-withdrawal model, people who learned better from rewards tended to show greater asymmetry of D₂ dopamine receptor binding favoring the left hemisphere, in both frontal lobe and basal ganglia regions, compared to people who learned better from punishments (see [Figure 12.24](#)).

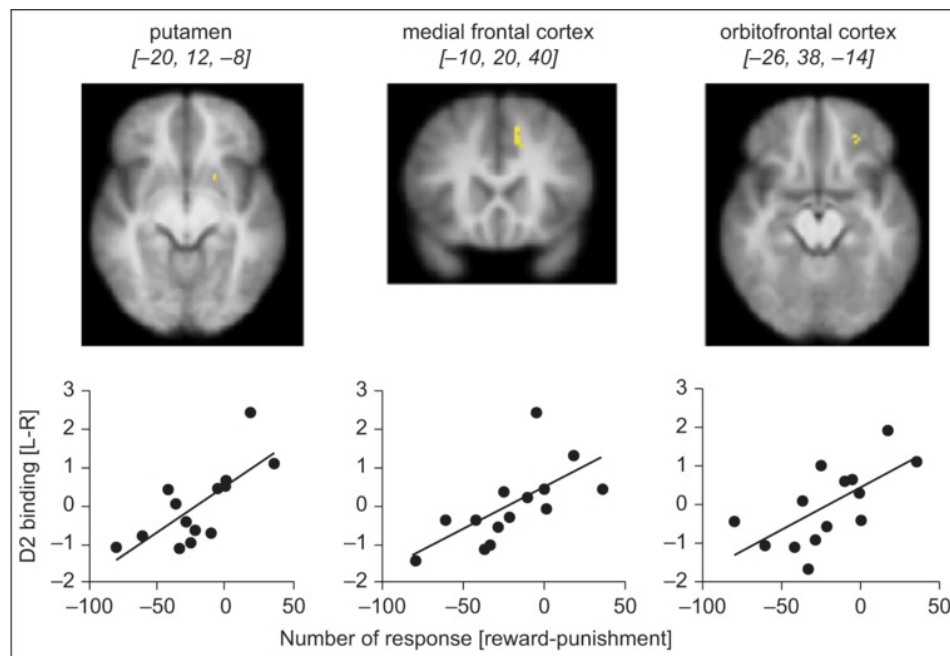


Figure 12.24 Asymmetry of dopamine binding is associated with tendency to learn from reward versus punishment.

Researchers measured asymmetries in D₂ dopamine receptor binding between the left and right hemispheres of the brain in people who completed a task that measured whether they tend to learn better from rewards (e.g., gaining points for correct responses) or from punishments (e.g., losing points for mistakes). In both subcortical regions (putamen/basal ganglia) and frontal cortex regions, greater asymmetries in dopamine receptors favoring the left hemisphere were associated with greater tendencies toward reward-based learning.

(from Tomer et al., [2014](#))

Approach and withdrawal might seem synonymous with positive and negative emotions, respectively. However, there is one emotion that does not quite fit this picture: anger. Anger is certainly a negative emotion, but it can be expressed either by “approach” behaviors, such as lashing out, or by withdrawal behaviors, such as giving someone the cold shoulder. For this reason, anger presents a unique test case for the approach-withdrawal model. If the model is correct, then people who tend to act out when angry should exhibit more left frontal activity. Studies have yielded results

generally consistent with this prediction, supporting the approach-withdrawal model (Harmon-Jones, [2004](#), [2007](#)).

Another cognitive neuroscience model of emotional experience incorporates a second dimension, the dimension of arousal (Heller, [1993](#); Heller and Nitschke, [1998](#)). The model is based on evidence that emotions are best described by two fundamental dimensions: valence (pleasant versus unpleasant) and arousal (high versus low intensity) (e.g., Feldman-Barrett and Russell, [1999](#)). For example, the emotion of sadness is not simply a condition favoring withdrawal (or negative emotion) over approach (a positive emotion); it is also a condition characterized by low levels of arousal. Likewise, a positive emotional state can be either high-arousal (excitement, elation), or low-arousal (calmness, contentedness).

How does the valence-arousal model differ from the approach-withdrawal model? The two models are very similar in their predictions for frontal regions. According to the valence-arousal model, the left frontal region is specialized for positive emotions and the right for negative emotions. However, the valence-arousal model also posits that arousal, or emotional intensity, is reflected in activity of posterior sections of the right hemisphere. Studies examining perceptual asymmetries have shown that emotional stimuli have a greater influence on heart rate, blood pressure, and the release of stress hormones when they are presented to the right hemisphere rather than the left (e.g., Wittling and Pflüger, [1990](#); Wittling et al., [1998](#)). Similarly, a recent study applied a noxious cold stimulus to either the left or right side of the body, and found that the left-side application (which would be perceived by the right hemisphere) resulted in greater heart rate and skin conductance changes than the right-side application (McGinley and Friedman, [2015](#)). These results support the conception that the right hemisphere is more closely linked to sympathetic nervous system manifestations of arousal.

The valence-arousal model of emotion has been particularly helpful in differentiating the patterns of brain activity that characterize depression and anxiety (Heller et al., [2003](#)). Although both depression and anxiety are certainly unpleasant rather than pleasant mood states, they differ in the arousal dimension. Depression is

typically a low-arousal state, whereas anxiety is often a high-arousal state, and therefore they are likely to differentially involve the right hemisphere's posterior regions. We consider the brain regions involved in anxiety and depression in more detail in [Chapter 14](#).

While dimensional models of emotional experience have been successful in tying broad dimensions of emotional experience to fundamental brain systems, recent studies have taken an alternative approach that examines distributed activity across a wide range of brain regions during emotional states. Here, the idea is that different emotions may have “signatures” that are broadly distributed rather than tied to a single brain region or system. Studies taking this approach have used multivariate pattern analysis (see [Chapter 3](#)) in an attempt to identify patterns of brain activity that correspond with specific emotions (e.g., Kragel et al., [2016](#); Saarimäki et al., [2016](#); Touroutoglou et al., [2015](#)). Although researchers still disagree about the best way to interpret results of these studies, the results generally indicate that different emotional states are associated with unique yet highly overlapping patterns of activation. That is, different emotional states can be distinguished statistically based on their distributed patterns of brain activation, but they also share regions in common as well. For example, many emotional states are associated with increased activity in a “salience network” that includes portions of the insula and anterior cingulate cortex (Touroutoglou et al., [2015](#)).

When considering why brain activity associated with an emotional experience might be distributed across many sectors of the brain, it is helpful to remember that emotional experience does not exist in isolation from all of the other components of emotion that have been reviewed in this chapter. Rarely do we simply sit and feel an emotion. Rather, emotions are integrally associated with various changes in information processing and behavior. For example, imagine that you hear a loud clap of thunder while at the beach. You are likely to engage in a suite of cognitive and behavioral changes associated with a feeling of fear. You may activate the fight-or-flight response, mentally note your own racing heart rate, remember the last time you got caught in a

thunderstorm, alter your visual attention toward the skies and your auditory attention toward possibly new rumbles of thunder, attempt to regulate your feelings (“maybe that thunder is distant”), alter your facial expressions and tone of voice (assuming a worried expression and perhaps yelling, “Kids! Time to get out of the ocean!”), and make decisions about whether to pack up and go home or wait it out. Ultimately, any comprehensive understanding of emotional experience must take into account how all these aspects of emotion are integrated within the brain.

Summary

Subcortical Contributions to Emotion

- The hypothalamus mediates some of the physiological phenomena associated with emotional states, such as changes in autonomic nervous system and endocrine function that are associated with fleeing or fighting.
- The amygdala is involved in learning the emotional significance of information and in producing a quick, instinctive, emotional response. The amygdala can also influence how attention is directed to emotionally significant events.
- The ventral striatum, or nucleus accumbens, is important in reward-seeking behavior. It is especially responsive to unpredicted rewards and becomes active when a person is anticipating a reward.

Cortical Contributions to Emotion

- The insula is involved in representing internal body states that are relevant to emotion. It is also important for the coding for unpleasant tastes, and also plays a role in the experience and perception of disgust.
- The anterior cingulate is involved in integrating information regarding emotion, cognition and action. It is also involved in evaluating the motivational outcome of actions.

- Orbitofrontal cortex is involved in assigning value to items and actions. It is also involved in evaluating reward and punishment contingencies and in responding adaptively to changes in these relationships. Damage to the orbitofrontal cortex can lead to deficits in controlling (and exhibiting) behavior and emotion in a socially appropriate manner.
- Control of emotions depends upon interactions among cortical and subcortical brain regions. Suppressing an emotion appears to involve top-down control over subcortical systems such as the amygdala and hypothalamus.
- Temporoparietal regions of the right hemisphere are important for comprehending emotional information expressed in tone of voice or facial expression.
- The right hemisphere plays a predominant role in the expression of emotion, both producing prosody that is related to emotional affect and in governing the expression of emotion on the face.
- Positive affect is associated with more activity over the left than the right prefrontal cortex, whereas negative affect is associated with the reverse pattern (greater right prefrontal than left prefrontal activity).
- States of high arousal appear to differentially involve the right hemisphere, particularly in posterior regions.
- A particular emotional state may evoke activity across a widely distributed pattern of brain regions, because experiencing an emotion involves many components, including alterations in autonomic control, interpretation of bodily signals, actions, and alterations in attention and decision making.

Chapter 13

Social Cognition



Social Influence

Conformity

Social Norm Compliance

Understanding Other Minds

Imitation and Simulation

Theory of Mind

Empathy

Self Versus Other

Autism and Social Cognition

In Focus: The Pain of Rejection

Perceiving and Judging Social Groups

In-group-Out-group Effects

Stereotyping and Prejudice

Stereotype Threat

Summary

Something was going on between the other kids, something swift, subtle, constantly changing – an exchange of meanings, a negotiation, a swiftness of understanding so remarkable that sometimes she wondered if they were all

telepathic. She is now aware of these social signals. She can infer them, she says, but she herself cannot perceive them, cannot participate in this magical communication directly, or conceive the many-leveled kaleidoscopic states of mind behind it. Knowing this intellectually, she does her best to compensate, bringing immense intellectual effort and computational power to bear on matters that others understand with unthinking ease.

(Sacks, [1995](#), p. 272)

So writes the neurologist and gifted observer of human behavior, Oliver Sacks, in discussing the remarkable case of Temple Grandin, possibly the world's highest functioning person with autism. At the time of this writing, Grandin is an accomplished professor of animal science at Colorado State University, designer of facilities for managing cattle, and author of numerous books about her experience with autism. She has been the subject of a feature-length film (Temple Grandin, released in 2010 and starring Claire Danes) and was selected as one of Time magazine's 100 most influential people in the world in 2010.

Born in 1947 and diagnosed with autism at the age of 3, Grandin experienced a childhood quite different from most children. In addition to delayed language development, a tendency toward "sensory overload," and an experience of the world that was highly visual, she also experienced significant social deficits. In her interviews with Sacks and in her own writing, she describes her perplexity at the social world around her. In social interactions, she felt awkward, her timing was off, she didn't understand what excited or upset other people, and she found social relationships completely baffling. Sacks writes, "What is it then, I pressed her further, that goes on between normal people, from which she feels herself excluded? It has to do, she inferred, with an implicit knowledge of social conventions and codes, of cultural presuppositions of every sort" (Sacks, [1995](#), p. 270).

Temple Grandin's story has been tremendously influential in providing a voice for people with autism. Cases like hers also give us deeper insight into the social abilities that we take for granted unless they are altered or absent. To detect social cues, to make inferences about others' internal feelings and perspectives, to understand and comply with social conventions – these abilities are a continuous part of our daily lives, and they can seem effortless, but yet they depend upon complex neurocognitive processes that are yet to be fully understood.

Why is the primate brain so large, in comparison to brains of other species? Even when adjusted for body size, primate brains, and particularly their frontal cortices, are disproportionately big. We might hazard a guess that large brains evolved in primates such as monkeys, apes, and humans, in order to support greater intelligence, flexible problem solving, or the ability to contemplate and plan for the future. But that just raises the question of why those capacities evolved. Surely they did not evolve so that primates could score well on standardized tests and get into a good college. What kinds of evolutionary problems, then, did large brains, and the capacities of intelligence that those large brains support, allow primates to solve? Many scientists now contend that the answer lies in understanding the social world of primates.

The social brain hypothesis posits that large brains were advantageous during evolution because they allowed primates to navigate the complex social relationships that group living entails (e.g., Dunbar and Shultz, [2007](#)). A comparison between birds and primates can illustrate this point (Dunbar, [2009](#)). Many species of birds form social relationships in that they bond with a partner and raise their young with that partner. For example, imagine a pair of cardinals that mate and then together feed chicks in their nest. Such pair-bonding is an important aspect of social life for many birds. In comparison, a monkey needs to navigate relationships not only with a single mate, but also with every other member of the living group, which might range from five to 50

other monkeys. As the group size increases, the number of relationships also increases, and therefore the cognitive demands of managing those relationships increase as well.

Group living requires expanded social skills. In order to reap the benefits of group living, such as shared food, a monkey (or a person) has to cooperate with other members of the group. Cooperation requires communication, possibly driving the evolution of language as well as nonverbal communication skills. Cooperation also requires memory of past encounters with a particular member of the troop, and it requires the ability to understand the goals and intentions of another member. Is that approaching monkey the one who gave me such a nice bout of grooming yesterday? Or is he the one who ran away with my banana?

Moreover, living together with others in the same territory requires resolving conflicts over resources. If another monkey and I both see a delicious piece of fruit hanging from a branch, do we fight over it? How do we resolve our conflicts without tearing one another to pieces? Dominance hierarchies, which are one mechanism of resolving conflicts over resources, require animals to remember which other animals out-rank them, and to act differently toward those “higher-ups” than toward lower-ranking animals. For example, if the alpha male and I both see the same piece of fruit, I will likely leave it for him to take, in deference to his higher rank, whereas I might take the fruit from a lower-ranking animal. The formation of social alliances, another mechanism of conflict resolution, calls upon complex memories of which other animals have been allies in the past. Forming alliances also requires a “third-party” understanding of the relationships between other animals. For example, I might recruit two specific monkeys for my alliance because I know that they get along well with each other.

According to the social brain hypothesis, the primate brain, and particularly its neocortex, expanded over evolutionary time due to just these kinds of selective pressures induced by group living. The ability to engage in flexible problem solving, rather than inflexible stimulus-response behavior, allowed monkeys and apes to gain more from group living and mitigate the costs of group living in ways that had survival

advantages. Theorists argue that these survival advantages must have been significant in order to offset the substantial metabolic costs of supporting a large brain (Dunbar and Shultz, [2007](#); Silk, [2007](#)).

Although direct evidence of events that unfolded over millions of years is hard to obtain, indirect evidence supports the social brain hypothesis. For example, when comparing brain sizes across species of monkeys and apes, there is a positive correlation between neocortex size and the average group size (Dunbar, [1992](#)). Primate species who typically live in larger groups tend to have a larger neocortex (when adjusted for overall brain size) compared to primate species who typically live in smaller groups (see [Figure 13.1](#)). Interestingly, the cross-species correlation between brain size and group size seems to be true only for primates, and not for other categories of species that have been studied. For example, among ungulates (hooved animals), there is no relationship between the typical size of the herd and the typical size of the brain for that species. This suggests that it is not simply living in a large group (as wildebeests do, for example) that matters; rather, it is the particular kinds of social problem-solving characteristic of primate groups that in some way accounts for the larger brains among group-living primates.

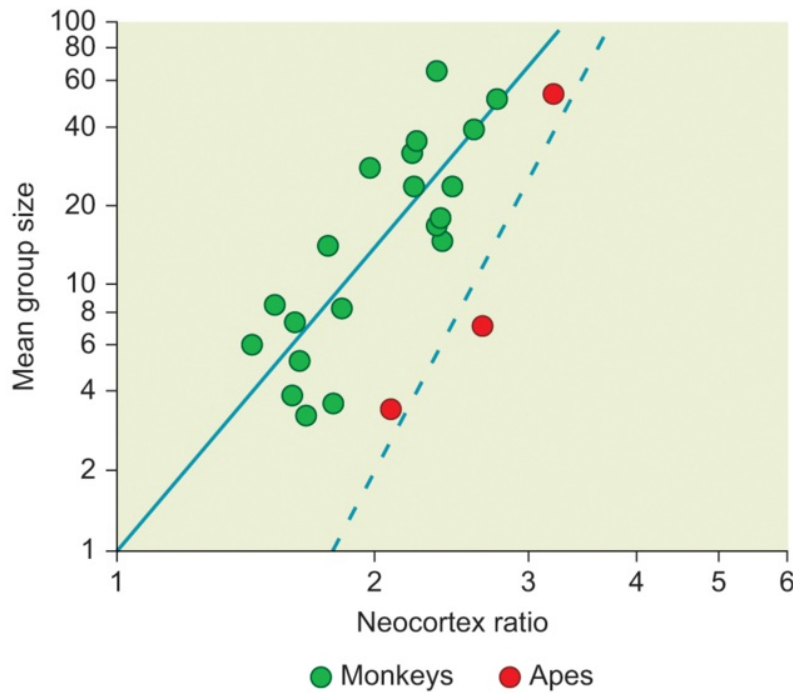


Figure 13.1 Association between social group size and cortex size.

Across primate species, the average size of social groups is correlated with the neocortex size, calculated as the ratio of neocortex volume to whole-brain volume.

(Dunbar and Schultz, [2007](#))

If the social brain hypothesis is true, then understanding the neural basis of social cognition is an essential task for the cognitive neuroscientist. In this chapter, we take a closer look at the cognitive processes involved in social interaction. We take as our starting point the general concept that the brain's cognitive processes usually unfold within a social context, and that, most likely, social factors were an important driver of brain evolution within primate species such as ours. Of course, social psychologists have long argued that social forces shape human behavior. The emerging area of social cognitive neuroscience goes further in examining the neural mechanisms by which social information influences behavior and by which the brain represents information about other individuals and social groups.

In the following sections, we consider a broad range of social cognition processes and review what is known about the implementation of those processes in the brain. Our topics include how individual cognition, judgments, and behavior are influenced by the

people around us, how we understand the beliefs and intentions of other people, how we empathize with the feelings of others, and how we make judgments about the social groups to which other people belong. As we will see, a distributed set of brain regions supports all of these functions. In some cases, general-purpose mechanisms such as frontal lobe cognitive control regions are recruited to support social cognition, whereas in other cases, specific brain regions— such as temporoparietal junction and medial prefrontal cortex (mPFC) – appear to be preferentially activated by the social aspects of information processing. Throughout this chapter, we can see how the phrase “the social brain” can be used not only as a hypothesis about how the primate brain evolved, but also as a characterization of interconnected brain networks that support our ability to think about the social world.

Social Influence

A key insight from decades of research in social psychology is that our thoughts, attitudes, beliefs, and actions are influenced by other people. The music you listen to, the movies you see, the hobbies you enjoy, the teams you root for, the political beliefs you hold – all of these are shaped by the beliefs, opinions, and actions of others. Others can shape our opinions even from a distance, for example through the now-ubiquitous electronic social media. In fact, even your perceptions of the visual and auditory stimuli around you are affected, in part, by what other people say that they can see and hear. Social psychologists refer to this general phenomenon as [social influence](#). Social influence can include both the ways that our individual judgments are shaped by the opinions of others and the ways that we understand and abide by the often unwritten rules of etiquette that govern social behavior.

Conformity

[Conformity](#) is the tendency for people to shift their own opinions, beliefs, and actions such that they are in agreement with other people. Psychologists have studied conformity

since the classic studies of Solomon Asch, who found that people's judgments about something as simple and concrete as the length of line segments could be influenced by the judgments of other people (e.g., Asch, [1951](#)). That is, participants in Asch's studies would often agree with others that a particular line best matched a target, even when it clearly didn't ([Figure 13.2](#)).



Figure 13.2 Classic studies of social conformity by Solomon Asch.

These experiments required participants to perform a simple line-matching task after hearing answers given by others, who were confederates in the research. In the example shown, imagine that five men around the table say aloud that line A best matches the sample line shown on the left. The sixth man, the actual participant in the study, is inclined to conform to their expressed opinions even though line C is the best match.

Social psychologists have proposed two general reasons why people conform to the opinions and behaviors of others (Cialdini and Goldstein, [2004](#); Toelch and Dolan, [2015](#)). The first is called [informational conformity](#), and the basic idea is that in many ambiguous or uncertain situations, we can rely on other people's opinions as a helpful source of information. For example, imagine that you are a monkey at risk of predation by leopards. If other monkeys in your group act like they are seeing a leopard nearby, it can benefit you to act like you see it too (flee or take cover!), whether or not you actually see it. To use another example, imagine that you are working through difficult math problems with a group of friends. If you are uncertain of your answer, and you notice that all your friends have worked through the problem and gotten the same answer

as one another, you may assume that their answer is correct. Here you are using their beliefs as a source of information. Of course, that doesn't mean that other people are always correct! But if the group is correct more often than not, it can help us in the long run to be influenced by information from the group.

The second main reason why people may conform is to be liked better by others, a motivation that social psychologists call **normative conformity**. In many situations in which we conform to the attitudes or beliefs of others, there actually is no "correct answer." For example, imagine that all your friends like the Pittsburgh Steelers football team and dislike the Cleveland Browns; or imagine that all your friends like classical music and detest jazz. By agreeing with their opinions, you're not necessarily arriving at "correct answers" about teams or styles of music. However, your friends may like you more if you agree with them. Because group belongingness is so essential to humans and other primates, the reward of being socially included and building group cohesion may sway our attitudes, beliefs, and actions to conform to those of the group.

While social psychologists have been studying conformity for decades, in recent years cognitive neuroscientists have gotten into the game as well (for reviews, see Schnuerch and Gibbons, [2014](#); Stallen and Sanfey, [2015](#)). For example, researchers have investigated the neural mechanisms by which people detect that their own opinions deviate from the social group norm and adjust their behavior accordingly. Perhaps not surprisingly, neural systems of cognitive control are implicated. As we learned in [Chapter 11](#), frontal lobe regions of executive control are important in detecting deviations from goals – such as errors or high-conflict situations – and then implementing needed behavior change. Therefore, it makes sense that these regions would be important in adjusting behavior to conform to others.

One of the first studies to examine conformity from a neuroscience perspective made use of a task in which participants had to rate the attractiveness of faces presented on a screen (Klucharev et al., [2009](#)). Participants viewed a face, rated the attractiveness of the face, and then received fictitious feedback about how other people had rated that

same face (see [Figure 13.3](#)). Then, at a later point, participants had the opportunity to rate the same faces again. Consistent with the general principle of conformity, participants' ratings shifted in the direction suggested by the (fictitious) rating of others. Moreover, activity in the medial prefrontal cortex (specifically, the posterior portion of the rostral cingulate zone) was increased when participants received the feedback that their ratings were different than those of others ([Figure 13.4A](#)). Other studies have found that this region is activated by tasks requiring decision making in the face of conflict. Similarly, ERP studies have found that feedback that one's ratings differed from those of the group evoked a feedback-related negativity, the same ERP signal evoked in other studies by feedback indicating an incorrect answer (Kim et al., [2012](#); Schnuerch and Gibbons, [2015](#)). That is, even though there is no "right answer" on a task such as rating facial attractiveness, participants' brains acted as if socially deviant answers were errors.

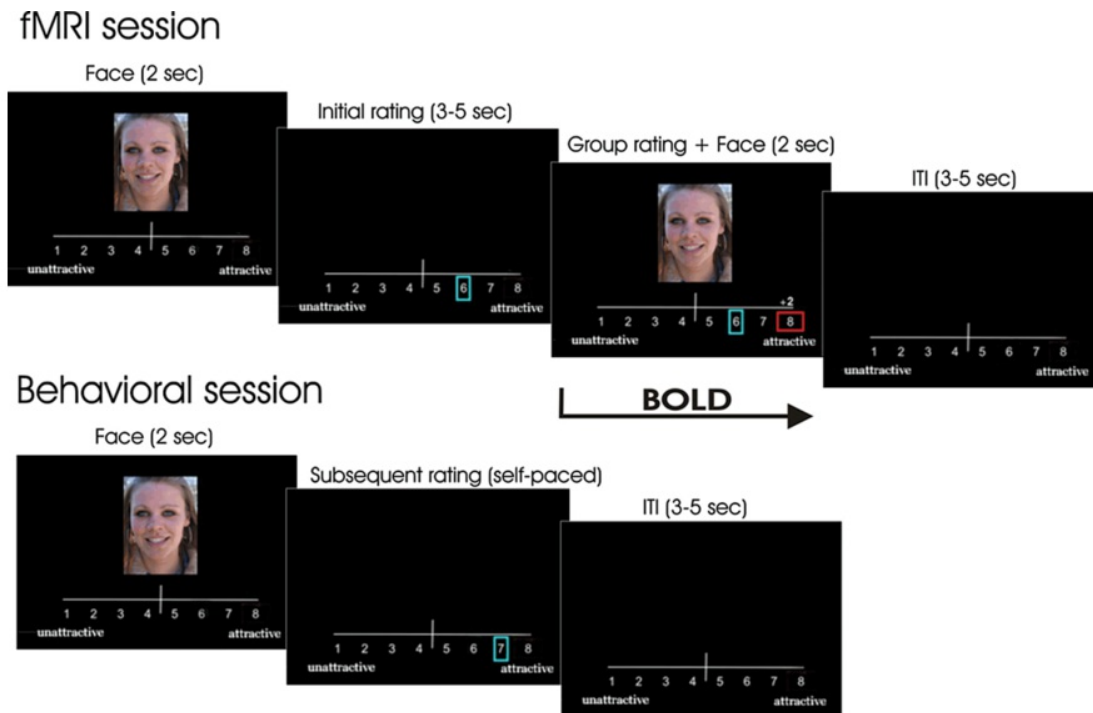


Figure 13.3 A task used to assess conformity behavior in neuroimaging studies.

The participant views a face for 2 seconds, and indicates how attractive the face is (in this example, the participant rates the face as a 6 on a scale from 1 to 8). The participant then receives feedback, in the form of a red square around one of the rating numbers, indicating the average rating of a fictitious group of peers. Here, the average peer rating is 8, which deviates from the participant's own rating. In a subsequent part of the study, participants rate the faces again, and their ratings tend to shift in the direction of the fictitious peer group opinion.

(from Klucharev et al., [2009](#))

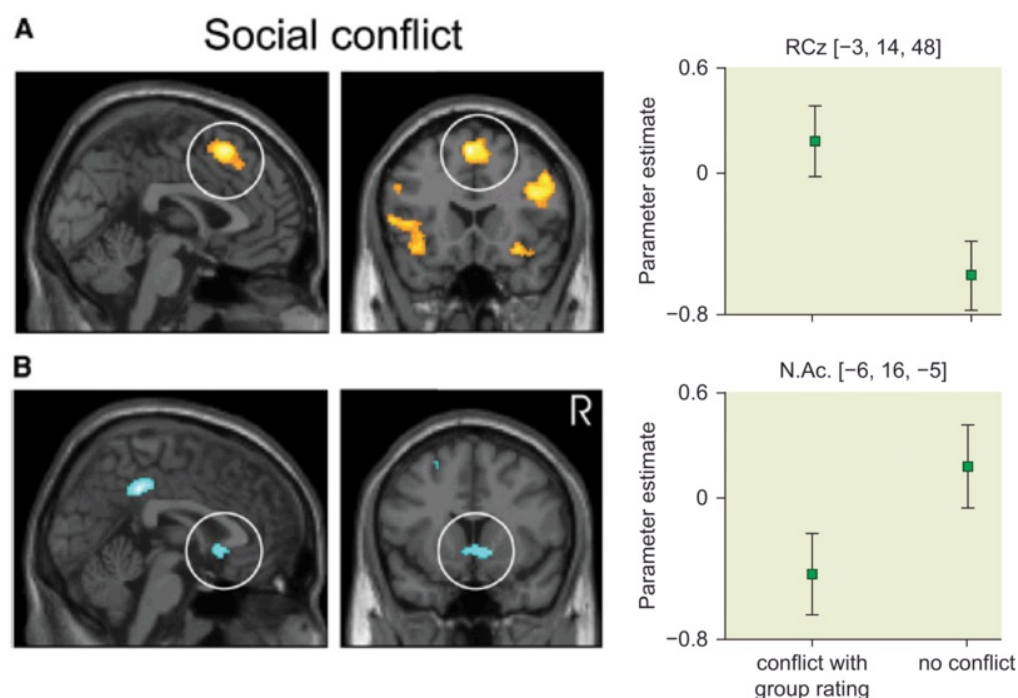


Figure 13.4 Changes in brain activity in response to social feedback.

This figure illustrates brain activity that increases (top row) or decreases (bottom row) when there is conflict between the participant's rating and the rating of a fictitious peer group in the task shown in [Figure 13.3](#). When the participant's own rating conflicts with the peer group, there is (A) increased activity in the posterior portion of rostral cingulate zone (RCZ) an area involved in decision making and conflict and (B) decreased activity in the nucleus accumbens (N.Ac.), an area involved in reward processing, compared to when the subject's rating agrees with the fictitious peers' ratings.

(Klucharev et al., [2009](#))

Just as social disagreement may be perceived as an “error,” social agreement may be perceived as a rewarding, positive outcome. Supporting this idea, feedback indicating that one's own opinions agree with a social group produces increased activity in the ventral striatum, a region known to be important in reward processing and reinforcement learning ([Figure 13.4B](#); Campbell-Meiklejohn et al., [2010](#); Klucharev et al., [2009](#); see also Jones et al., [2011](#)). Furthermore, administration of a dopamine agonist has been shown to increase conformity (Campbell-Meiklejohn et al., [2012](#)).

Because dopamine in the ventral striatum is known to support reward-related behavior (as we reviewed in [Chapter 12](#)), this finding fits with the idea that dopaminergic reward regions contribute to conformity behavior.

Other studies have used neural measures to examine how information is processed differently when it has previously received a social stamp of approval. For example, one study examined ERP responses to stimuli for which the participant had previously agreed or disagreed with a fictitious social group (Schnuerch and Gibbon, [2015](#)). The amplitude of the P2 response, indexing early attention to the stimulus, was greater if the participant had previously received feedback indicating that his or her rating of the stimulus was consistent with the group's judgment (compared to stimuli in which the feedback indicated that the participant's rating was inconsistent with the group). This evidence implies enhanced attention to stimuli when the individual's prior judgment has been validated through group agreement.

To directly examine the brain regions that influence social conformity, researchers disrupted brain activity using TMS (Klucharev et al., [2011](#)). Participants rated the attractiveness of faces and received feedback about social agreement or disagreement with each rating (similar to the task shown in [Figure 13.3](#)). Just before performing the task, the participants received either TMS that disrupted activity in the medial prefrontal cortex (mPFC), sham TMS, or TMS to a control region thought to be uninvolved in social processing (parietal cortex). Medial prefrontal cortex was targeted because of the prior evidence that this region was activated in response to feedback indicating social disagreement (Klucharev et al., [2009](#)). Compared to both of the other conditions, TMS to the mPFC disrupted conformity behavior, reducing the amount that participants' subsequent ratings of the faces were influenced by the fictitious peer feedback. This study implies that mPFC plays a causal role in processes that influence us to conform to the judgments of others.

Social Norm Compliance

Our behaviors are also subject to social influence in the form of social norms, which are written and unwritten rules that govern social behavior. Some social norms may take the form of unstated rules of etiquette, such as how to behave properly at the dinner table, what to wear to a funeral or a job interview, or how much eye contact to make with other people on the subway. Other social norms are codified in the form of laws, which can include prohibitions against stealing, assault, or arson, for example. Social norms and expectations are learned, and some norms may vary between cultural groups. For example, in some cultures people stand quite close to one another in conversation, whereas in other cultures more distance is considered socially appropriate. Multinational companies often spend time training their personnel on appropriate modes of behavior in different countries, to avoid unknowingly insulting their business partners. Violations of social etiquette can be awkward and result in misunderstanding and possible loss of social status, whereas violations of codified norms, such as laws, can result in explicit punishment in the form of fines or even imprisonment.

Although we may at times chafe against the restrictiveness of social norms – such as when forcing one's foot into an uncomfortably fancy shoe for a wedding, or, more seriously, considering civil disobedience against laws perceived to be unjust – social norms serve to regulate behavior in ways that may be generally functional for a social group. Some social norms, such as those against stealing or assault, are necessary to protect group members. Others, such as rules of etiquette, may help to define group membership or increase social cohesion through expressions of respect between members. In any case, understanding social norms is an important task for anyone living in a social group.

Many studies have detailed impairments in understanding and complying with social norms among various clinical patients. Behavior deemed “socially inappropriate” has been described in patients with traumatic brain injury, particularly when frontal lobe damage is implicated (e.g., Spikman et al., [2012](#)). For example, neuropsychologist Jenni Ogden describes a patient with severe frontal lobe damage who would often shout and

swear at others in her hospital ward and would sometimes undress in the presence of visitors (Ogden, [2005](#)). Socially inappropriate behavior is also observed in patients with some kinds of dementia, particularly in those with frontotemporal dementia, who often display socially disinhibited behavior and loss of tact or manners (Bickart et al., [2014](#); see [Chapter 16](#)). Violations of social norms are also seen in neuropsychiatric conditions such as Tourette's syndrome (e.g., Channon et al., [2012](#)), in which individuals may shout out words considered obscene or blasphemous. Moreover, as seen in the opening vignette of this chapter, individuals with autism are often characterized by difficulty in understanding social norms and expectations.

Alterations in social behavior in patients are often measured only by a clinician's global evaluation or a family member's anecdotal report, so it can be difficult to tell exactly what cognitive process (or processes) may be disrupted. Perhaps the patient has a faulty perception of social cues, thus limiting the ability to use those cues to guide behavior. Perhaps the patient has lost stored representations of social norm information, analogous to a memory impairment. Or, the patient may have a solid understanding of the social norm but she may suffer from an inability to inhibit an inappropriate action. Another possibility is that the patient has intact internal representations of social cues and norms, and an intact ability to exert inhibitory control, but has lost social motivation and no longer cares about the social rewards or costs related to behavior. Because compliance with social norms is a complex, multicomponent process, it can break down in any number of ways.

Damage to orbitofrontal cortex (OFC) has been most strongly associated with alterations in social behavior and judgments. For example, in one study, patients with damage to the OFC, as well as patients with lateral frontal lobe damage and healthy controls, were each videotaped in a conversation with a stranger (Beer et al., [2006](#)). Later, the patients watched the videos and made evaluations of the appropriateness of their own behavior, specifically focusing on their level of self-disclosure of personal information to the stranger. Independent raters judged the OFC patients' behavior as less

appropriate than those of the two comparison groups, but the patients themselves did not, suggesting that they had poor insight into their own degree of social norm violation. Patients with damage to the OFC were also impaired on tasks that required them to judge whether or not a narrative vignette included a social faux pas, such as one person unintentionally saying something that hurt another person's feelings (Leopold et al., 2012). As we discussed in [Chapter 12](#), the OFC is thought to be critical in incorporating emotional information into decision making. Because normal social interactions likely depend upon making use of emotional cues (such as facial expressions and prosody), disruption in the ability to appropriately integrate those cues could potentially lead to impaired social decision making.

Neuroimaging studies of social norm compliance have tended to focus on certain economic games in which social norms of fairness are critical in the game. For example, several studies have made use of the “ultimatum game,” also known as the “take it or leave it” game. In this game, one player (the “giver”) decides how to split a reward (e.g., valuable points or money) between herself and another player, the “receiver” ([Figure 13.5](#)). The fair action is to divide the reward evenly between the players, and people generally expect that others will follow this fairness norm in sharing. Deviations from the fairness norm, in the form of an unfair split, are generally perceived as socially inappropriate. For example, imagine if you and your friend found a box of 10 delicious chocolates, and he gave you two and proceeded to eat the other eight himself.

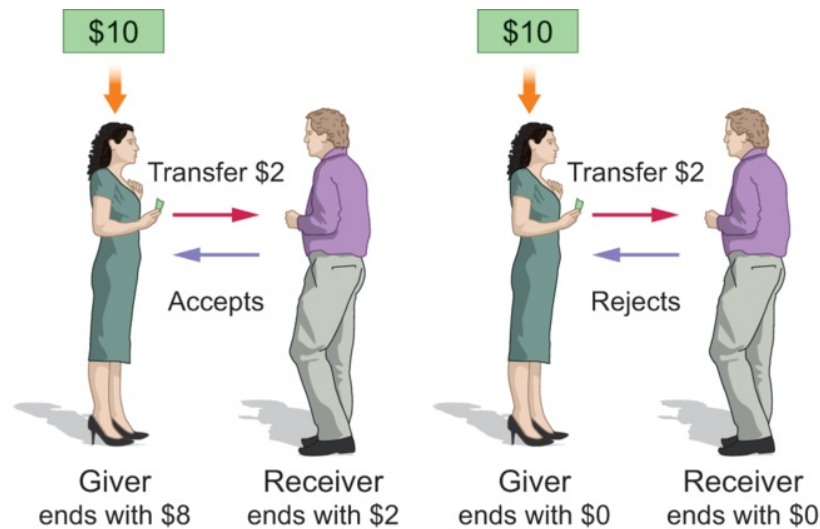


Figure 13.5 The ultimatum game.

This is a simple economic game in which one player, the “giver,” decides how to divide \$10 between himself or herself and a second person, the “receiver.” The receiver can then decide whether to accept the offer, in which case the reward is allocated according to the proposed split (shown on left), or to reject the offer, in which case neither participant receives any money (shown on right). Such games are used to study violations of the norm of fairness.

Economic games like the ultimatum game provide a useful way to study norm compliance because deviations from the norm can be quantified. For example, a 90:10 split of resources is more deviant from the fairness norm than is a 60:40 split. In addition, researchers can examine how the behavior of others is affected by violation of the fairness norm, because the games typically allow some form of retribution. Specifically, in most versions of the game, the player receiving the offer can decide to take it, in which case the reward is allocated according to the proposed split, or leave it, in which case neither player gets anything. Generally, people are more likely to reject an offer the more it deviates from a fair split ([Figure 13.6](#)). In this way, the consequences of violating social norms can be examined in ways that are more concrete than in many real-life social interactions.

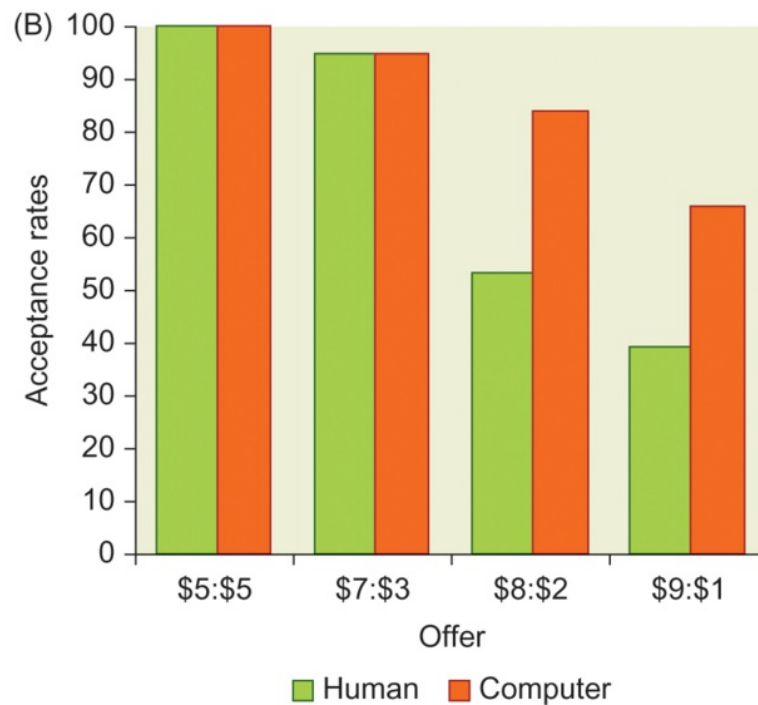


Figure 13.6 People are more likely to reject unfair than fair offers in the ultimatum game.

This graph depicts the likelihood of the receiver in the ultimatum game (see [Figure 13.5](#)) accepting the offer, as a function of the split offered by the giver. The rates of acceptance decrease as the offer becomes less fair. Also, unfair offers are less likely to be accepted when the receiver thinks that the giver is another human, as opposed to a computer program.

(Sanfey et al., [2003](#))

Neuroimaging studies of the ultimatum game (and related economic games) have revealed a few key findings. First, consistent with the unpleasantness of being treated unfairly, activity in the anterior insula of the receiver increases with increasing levels of unfairness of an offer (Sanfey et al., [2003](#); see also Chen et al., [2015](#)). This could be expected given the role of the insula in registering disgust (see [Chapter 12](#)). Interestingly, the insula's response to an unfair offer from another person was greater than to that same unfair offer when the receiver thought it was coming from a computer (Sanfey et al., [2003](#)). This underscores the interpersonal element of the fairness norm and its perceived violation. Moreover, the same study found that activity in anterior

cingulate and dorsolateral prefrontal cortex also increased in the recipients when they received an unfair offer, compared to a fair offer. These increases could be due to the greater demands on cognitive control when making a decision about whether to reject an unfair offer.

A second set of findings pertains to the “giver,” the person who is deciding whether to make a fair or unfair offer. The giver tends to make fair offers more frequently in versions of the game in which the receiver has the option to punish unfair offers (as opposed to simply choosing not to accept them), such as withholding monetary units in retribution. Interestingly, this tendency to adhere to the fairness norm under threat of punishment is associated with increased activity in frontal lobe regions, including lateral OFC and dorsolateral regions, in the giver (Spitzer et al., [2007](#)). These frontal regions were more activated in givers during the threat-of-punishment condition compared to a control condition with no punishment, and the difference in activity between conditions was greater for givers who also altered their behavior more, giving more under the punishment than control condition. Thus, these frontal regions appear to be important in incorporating information about the threat of social retribution when deciding how much to share.

A recent stimulation study further addressed the causal importance of lateral prefrontal cortex (LPFC) in social norm compliance (Ruff et al., [2013](#)). Researchers applied tDCS to LPFC while participants made offers in the ultimatum game, deciding how much to share monetary units with another player. Anodal tDCS was applied to increase activity in the LPFC and cathodal tDCS was applied to decrease the activity; both were compared to a sham control condition. Under conditions in which the receiver could apply a punishment in monetary units, enhancement of LPFC activity in the giver led the giver to share more money, whereas suppression of LPFC activity led the giver to share less ([Figure 13.7](#)). The researchers concluded that, at least in the presence of possible sanctions, LPFC activity causes greater compliance with the fairness norm.

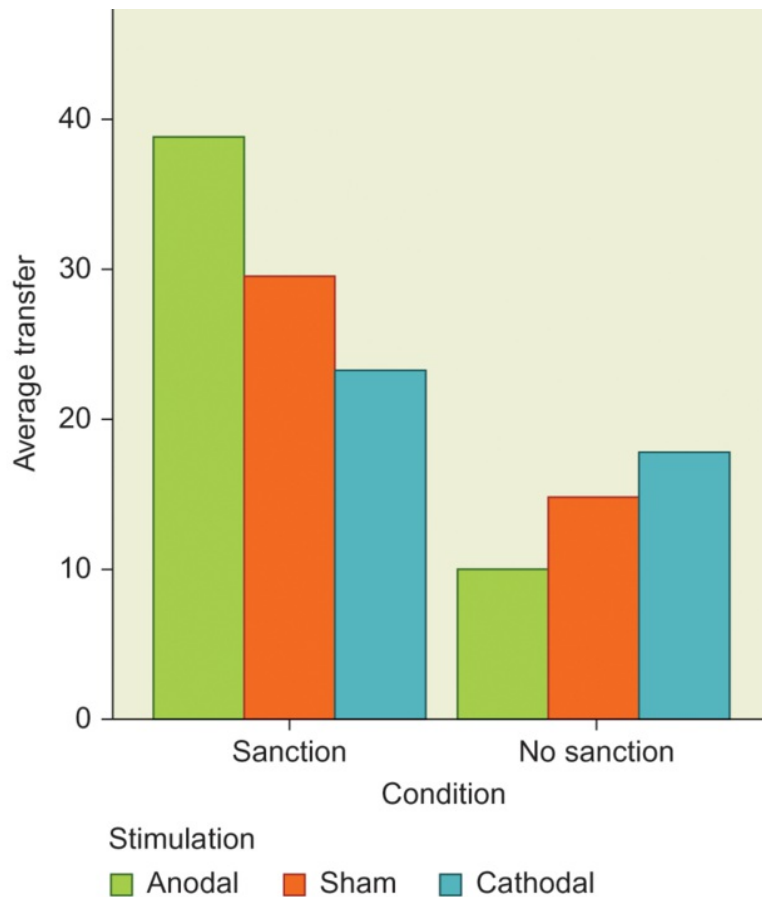


Figure 13.7 Brain stimulation affects the amount of money shared in the ultimatum game.

“Givers” in the ultimatum game make different offers depending on activity in the lateral prefrontal cortex (LPFC) and depending on whether the receiver has the opportunity to punish the giver by rejecting unfair offers. Under the possibility of sanctions (punishment by the receiver), increasing LPFC activity by anodal tDCS stimulation increases the amount of money offered by the giver, and decreasing LPFC activity by cathodal stimulation decreases the amount of money offered (left side of graph). When there is no possibility of punishment (no sanction) for unfair offers, the giver offers less money overall, and, moreover, LPFC excitation decreases offers and LPFC inhibition increases offers (right side of graph). These results suggest that LPFC plays a different role in sanctioned versus voluntary norm compliance.

(originally from Ruff et al., [2013](#); adapted in Sanfey et al., [2014](#))

Interestingly, though, in the condition in which the receiver could not apply any punishment, LPFC stimulation of the giver had exactly the opposite effect: increasing activity in LPFC led to decreased sharing, whereas decreasing activity led to increased sharing ([Figure 13.7](#); Ruff et al., [2013](#)). Thus, in a somewhat puzzling pattern, the results imply that LPFC plays a different and even opposite role in “sanctioned” norm compliance (in which explicit monetary punishment can be leveled against unfair offers) than in voluntary norm compliance (in which the only reason to share is that it seems the right thing to do). Specifically, increased LPFC activity caused more sharing under threat of punishment but less voluntary sharing, suggesting that perhaps increased LPFC activity is associated with more “Machiavellian,” calculating, or selfish approaches. More generally, these results imply that understanding the role of LPFC in norm compliance must take into account the participant’s motivation, namely, whether compliance is driven by internalized norms or by avoidance of explicit punishment.

For the purposes of examining the mechanisms of social norm compliance, the quantitative, economic nature of games such as the ultimatum game has both advantages and disadvantages. As discussed above, there are advantages in being able to quantify the level of compliance and social cost in monetary units. This reduces the nebulous idea of “social inappropriateness” to numbers, which can be appealing in its simplicity. In such games, it is also clear what “winning” means; that is to say, there is an optimal strategy that produces the most points. Compare this to actual social situations, though. What is the “cost” of a social gaffe, such as standing too close to someone during conversation, failing to show respectful etiquette, or wearing the wrong outfit to an interview? Furthermore, does the goal of winning money in an economic game effectively model the social goals we may have, such as social inclusion or status? In the area of social norm compliance, as in many areas of human cognition and behavior, laboratory-based models can lead to important insights, but their limitations in modeling behavior in the natural world should also be acknowledged.

There is still much to be learned about the neural basis of social norm compliance, but one key point clearly emerges across the converging evidence from clinical, neuroimaging, and stimulation studies. Namely, the frontal lobes, including OFC, DLPFC, and ACC, are critically involved. This conclusion should not be surprising, because we already know that these regions are essential for cognitive control and decision making, and social norm compliance directly draws upon these processes. This set of findings is also fully consistent with the social brain hypothesis of primate evolution, which posits that the frontal cortex expanded over evolutionary time to support social cognition.

Understanding Other Minds

People are constantly trying to infer what other people are thinking about. You may wonder whether your roommate likes you, whether your boss intends to fire you, where your teammate is going to throw the basketball next, or whether your study partner really understands the course material he or she is explaining to you. All of these examples involve attempting to understand what is going on in the mind of another person.

There are two main theories of how we understand others' thoughts and feelings. One theory suggests that we understand the mental states of others through simulation. In the simplest sense, [simulation](#) just means acting like, or imitating, another person. For example, if you see another person crying, you might understand his mental state by starting to tear up yourself. By mimicking that other person's actions and expressions, you feel as he does, and therefore you comprehend his mental state.

Another approach, sometimes called [theory of mind](#), assumes that we have a cognitive representation of other people's mental states, including their feelings and their knowledge. Through these cognitive representations, we are able to hold in mind two different sets of beliefs: what we know, believe, or feel, and what we think another person knows, believes, or feels. For example, a neuroscience professor might know

how action potentials propagate in a neuron, while at the same time knowing that her students do not yet know this on the first day of class. (Thinking about others' knowledge can go even one step further: imagine a student who has already learned about action potentials, thinking "the teacher doesn't know that I know this already!")

It should be obvious that these two ways of understanding other people – simulation and theory of mind – are not mutually exclusive. For example, simulation can best explain emotional behaviors and motor actions that can be easily mimicked. It can also explain how emotions (and behaviors like laughing) can be "contagious" even among small children and less cognitively sophisticated animals. At the same time, if we only used imitation to understand other people, it could be difficult to separate our own feelings from those of others. Furthermore, the theory-of-mind approach can more easily explain how we represent mental states that do not have an obvious outward expression, such as beliefs and knowledge. Therefore, it is likely that we rely on both means of representing others' mental states, though perhaps in different circumstances. In the following sections, we consider evidence related to the neural mechanisms of simulation and theory of mind and consider how both of these concepts relate to the idea of empathy.

Imitation and Simulation

The phrase "monkey see, monkey do" describes the tendency of primates to engage in mimicry, or imitation of the actions of others (Chartrand and Lakin, [2013](#)). Some researchers argue that people are even more skilled at imitation than other primates (e.g., Iacoboni, [2009](#)). Human mimicry can be consciously intended, such as when a piano student attempts to model her teacher's fingering on the piano keys, or when a child plays "copycat" with another child. But mimicry can also occur without conscious intent, such as when two speakers engaging in a conversation match one another's gestures, talking speed, and facial expressions, without even being aware of doing so.

Imitation can contribute to social cohesion. People generally engage in more mimicry of their friends than of strangers, as well as more mimicry of likable strangers compared to unlikable strangers (Chartrand and Lakin, [2013](#)). Furthermore, people are more likely to engage in mimicry when they are primed with pro-social words like affiliate, friend, together (Lakin and Chartrand, [2003](#); Leighton et al., [2010](#)) or when they have just experienced social exclusion and therefore have a stronger desire for affiliation (Lakin et al., [2008](#)). Imitation can also affect how much we like others. For example, when people were prevented from mimicking an interaction partner, their liking of that person was decreased (Stel and van Knippenberg, [2008](#)). Imitating facial expressions can help us to identify the emotions of another person. For example, one study prevented imitation of facial expressions by temporarily paralyzing facial muscles with Botox injections and found decreased ability to identify the facial expressions of others (Neal and Chartrand, [2011](#)).

The neural mechanisms of imitation likely depend in part on mirror neurons, which we learned about in [Chapter 4](#). Mirror neurons, as you recall, are neurons that fire both when an individual carries out an action and when he or she observes another individual carrying out the same action. Mirror neurons were first discovered in motor regions of the monkey brain, namely, in the inferior frontal lobe (e.g., Di Pellegrino et al., [1992](#); for diverse interpretations, see Cook et al., [2014](#); Hickok, [2013](#); Iacoboni, [2009](#)). Studies using implanted electrodes in human epileptic patients have also found that individual cells in supplementary motor cortex in the frontal lobe, as well as medial temporal lobe regions such as hippocampus, exhibit action-mirroring properties in the same way as the monkey mirror neurons (Mukamel et al., [2010](#)).

Mirror neurons seem like a plausible candidate for supporting imitation. Indeed, neuroimaging studies in humans have found that imitation of simple finger movements resulted in increased activity in inferior frontal cortex, the region where mirror neurons are found in monkeys (Iacoboni et al., [1999](#); see also Kilner et al., [2009](#)). Moreover, disrupting activity in inferior frontal cortex using TMS decreases the ability to imitate finger movements (Heiser et al., [2003](#)). Complementing this finding, another study found

that stimulating the inferior frontal cortex with tDCS increased the degree of motor mimicry in social interaction, whereas sham stimulation or stimulation to the temporoparietal junction (another region involved in social processing, see below) did not (Hogeveen et al., [2015](#)). Taken together, these studies support the idea that inferior frontal cortex plays an important role in motor mimicry.

When mimicry happens in real life, it usually happens in a complex social situation with many social cues present. For example, imagine that you are at a job interview, and the interviewer clasps her hands together in her lap. Are you likely to mimic the same posture? It may depend on whether other social cues, such as the interviewer's tone of voice, facial expression, handshake, and language, establish a sense of rapport. Though untangling the interaction among all of these cues is challenging, researchers have begun to address how mimicry is related to one very important social cue, eye contact.

Initial behavioral research indicated that establishing eye contact enhances the tendency to mimic another person (Wang, Newport, and Hamilton, 2011). The study made use of a paradigm in which participants were instructed, for a given set of trials, to make either open-hand or close-hand movements for that set of trials. On each trial within the set, an image of a person's hand was presented either opening or closing. On congruent trials, the hand movement in the video was the same as the instruction to the participant for the set (e.g., video of an opening hand during an open-hand set), and on incongruent trials, the depicted movement was different than the instructed movement (e.g., video of an opening hand during a close-hand set of trials). Imitation is indexed by the extent to which the participant's own hand movement is influenced by the other person's hand movement. In the behavioral study, participants showed a greater degree of imitation when they viewed an actress making direct eye contact before moving her hand, as opposed to when the actress was shown with an averted gaze (see [Figure 13.8](#)).





| | | Response | |
|------|---------|---|--|
| | | Congruent | Incongruent |
| Gaze | Direct |  CLOSE |  CLOSE |
| | Averted |  CLOSE |  CLOSE |

Figure 13.8 Sample stimuli from a task that assessed how eye contact influences imitation.

In a given block of trials, participants were instructed to make hand movements, either OPEN or CLOSE. (The example here refers to a CLOSE-hand block.) Videos could show either a hand movement congruent with the instruction (left column) or incongruent with the instruction (right column). Furthermore, the actress in the video either showed direct gaze (top row) or averted gaze (bottom row). Congruent hand motions were speeded when the actress was shown with direct gaze, indicating that eye contact facilitates imitation.

(from Wang et al., [2011b](#))

In subsequent fMRI research using the same paradigm, activity in three different brain regions was correlated with this effect of eye contact on imitation: superior temporal gyrus (known to be important in registering information about gaze direction), dorsal medial prefrontal cortex, and inferior frontal gyrus (Wang et al., [2011b](#)). That is, in each of these regions, there was enhanced activity when direct gaze (compared to averted gaze) was paired with congruent hand movements between self and other. Furthermore, modeling of the functional connectivity of these regions suggested that connections between them were enhanced under the condition of direct eye gaze, implying that direct gaze coordinates activity in these regions. Such results represent a step toward understanding how one particular social cue, eye contact, could enhance mimicry of actions.

The concept of mirror neurons originally developed in the context of understanding action execution and observation, but researchers have since broadened the concept of neural mirroring considerably beyond this initial emphasis on motor actions. That is, researchers have asked whether another person's mental states, not just their overt actions, are somehow mirrored in the brain of an observer. Indeed, in many situations, the same brain regions seem to be activated when a person experiences a particular state as when he or she observes another person experiencing that same state. For example, pain areas of the brain are activated when we see another person in pain (e.g., Jackson et al., [2005](#); Singer et al., [2004](#)), and disgust-related areas of the brain, such as the insula, are activated both when we smell foul odors and when we see another person smelling them (Wicker et al., [2003](#)). Likewise, observing a mistake made by another person generates a similar neural response from the anterior cingulate as making that mistake oneself (van Schie et al., [2004](#)). In these examples, sensory, emotional, and error-monitoring systems are activated by vicarious observation of another's experience, a phenomenon sometimes referred to as neural mirroring, "experience sharing," or "resonance."

Interestingly, the degree to which we simulate another's experiences may depend on social factors, such as how much we like that person or whether we see ourselves as similar to that person. One study found that a portion of the ventral striatum, the nucleus accumbens, was activated when participants viewed someone else receiving a large reward, but that such activity was greater when the person receiving the reward was deemed to be socially desirable, likable, and similar to the actual participant (Mobbs et al., [2009](#)). Likewise, in a study in which participants watched a confederate perform a simple computer task, the neural response to errors made by the confederate was predicted by the participant's judgment about the similarity between himself and the confederate (Carp et al., [2009](#)). These studies suggest that although we have the capability to mirror other people's states, we may do so preferentially for others whom

we see as similar to ourselves. In a later section, we will discuss the relationship of findings on imitation and simulation to the concept of empathy.

Theory of Mind

Theory of mind, or “mentalizing,” is the capacity to cognitively represent another person’s mental states, and even to understand that they may be different than one’s own. For example, consider the task illustrated in [Figure 13.9](#), sometimes referred to as the false belief task. In this task, the participant hears a scenario such as the following: Sally and Anne are playing in a room that has both a basket and a box. Sally puts her marbles in the basket, and then leaves the room. When Sally is gone, Anne (that trickster!) hides the marbles in the box. When Sally comes back to the room, where will she look for her marbles? As adults in full possession of theory of mind, we understand that Sally will look in the basket, where she left the marbles. We understand that Sally can have a false belief, one that we know to be wrong.

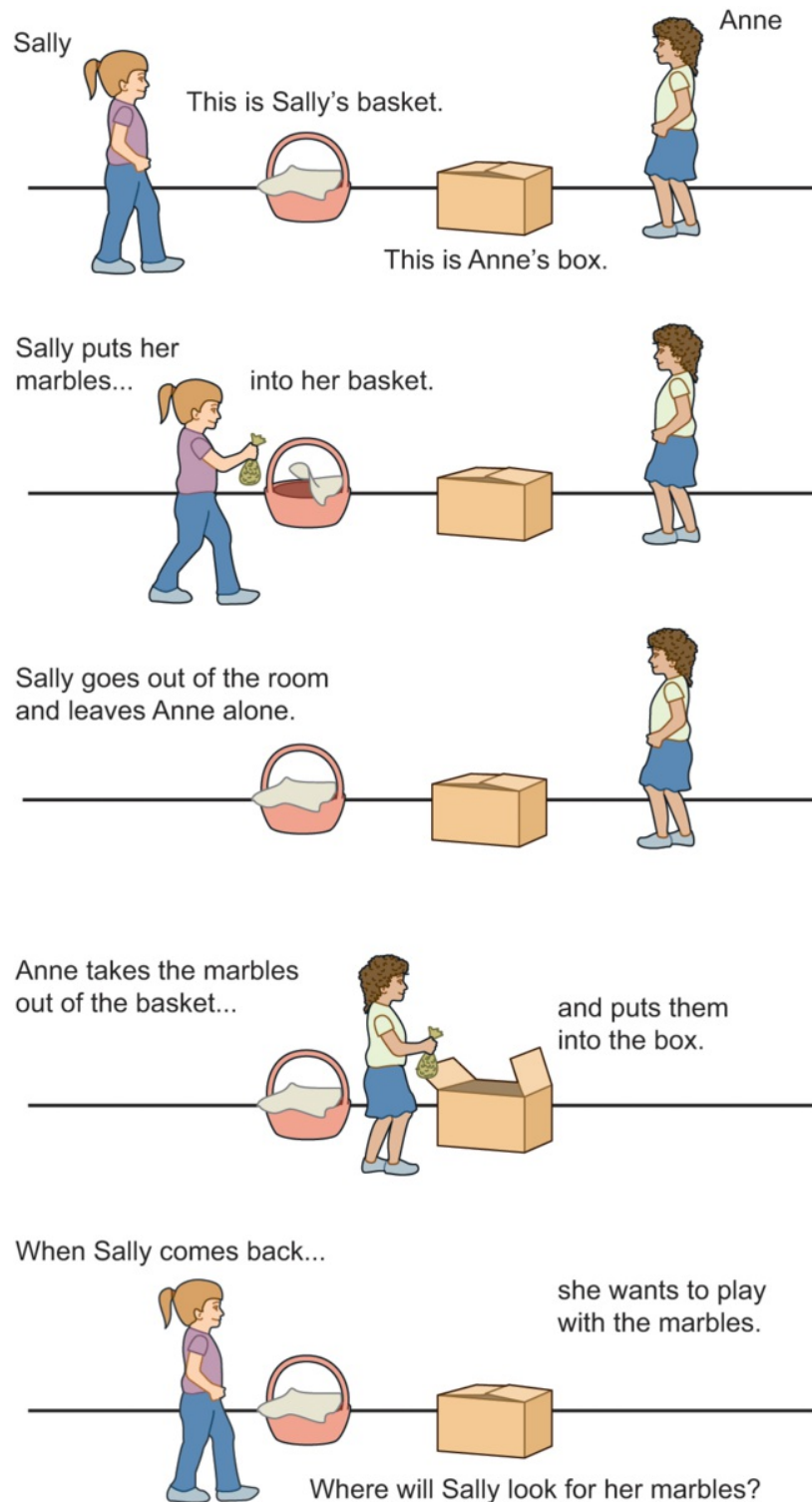


Figure 13.9 The false belief task often used to assess theory of mind.

Understanding that Sally will look for the marbles in the basket (rather than the box) depends on the ability to represent another person's knowledge as distinct from one's own knowledge.

In addition to supporting such higher-level reasoning about another's beliefs, mentalizing also involves the more fundamental ability to infer the feelings, goals, and intentions of other people. We easily grasp, for example, that people can feel sad but rocks or tables cannot. We also often make predictions about other people's desires, for example, understanding that a young child placed in front of a cookie jar will probably want the cookie inside. The cookie itself, however, doesn't "want" to be eaten, because it cannot have desires like humans and animals can have. And, we can understand that people can have goals or intentions. For example, when we drive on the highway and see the car in front of us start to speed up and edge toward the center dashed line, we infer that the driver (but not the car itself) intends to overtake the car ahead. In all these ways, we make inferences about other people's internal states of mind.

The ability to pass the false belief test is the most sophisticated demonstration of mentalizing because false belief reasoning involves thinking about another person's thoughts (not just their feelings or goals) and it has a counterfactual aspect (i.e., the ability to mentally represent both the true state of affairs and the false knowledge that a person may hold). Because of the high level of cognitive sophistication required for this kind of theorizing about another person's knowledge, this ability is not thought to develop until the late preschool years, although children are able to make simpler inferences about others' feelings and desires at younger ages (Flavell, [2004](#)). Some argue that the ability to cognitively represent the mental states of others is unique to humans and possibly great apes, though this topic is much disputed (e.g., Povinelli and Vonk, [2003](#); Tomasello et al., [2003](#); see also Brüne and Brüne-Cohrs, [2006](#)). One reason that theory of mind is so interesting is that it is necessary for intentional deception, or purposely misleading others to believe something that we know is wrong. Theory of mind is also relevant to other contexts, such as teachers evaluating their students' state of knowledge, and spouses understanding what their partners may expect for an anniversary gift.

So, what do we know about the neural processes underlying mentalizing skills? As you might expect, it is not easy to localize theorizing about another person's internal states to a particular brain region, because it is so abstract and probably involves several component operations. However, some studies have examined brain activity when people are required to make inferences about the feelings, intentions, or beliefs of other people (see Schurz et al., [2014](#), for meta-analysis). Below we consider three different types of task that have been used to assess mentalizing functions, so that we can compare the similarities and differences in results between them.

Some studies have taken advantage of a classic phenomenon in social psychology, the Heider-Simmel illusion, to study the neural underpinnings of the fundamental concept of animacy. Although we know that only humans and animals – and not inanimate objects – can have feelings and goals, we often attribute human-like mental states to objects when they move in certain suggestive ways. In an illusion first shown by psychologists Heider and Simmel ([1944](#)), when people view videos of simple geometric shapes moving around a box, they tend to attribute mental states to them. For example, people might think that one triangle is “hiding,” that another one is a “bully” who is chasing the first triangle, or that a shape is “angry” if it bashes into a wall repeatedly (see [Figure 13.10A](#)). fMRI studies have examined the neural correlates of such mentalizing by contrasting brain activation when viewing images such as the Heider-Simmel videos, in which shapes seem to be moving intentionally, to brain activation when viewing randomly moving shapes (e.g., Castelli et al., [2000](#)). Across several such studies, the temporoparietal junction was most consistently activated, with other common areas of activation including superior temporal and inferior frontal lobe ([Figure 13.11](#); Schurz et al., [2014](#)). As we will discuss in more depth later, the temporoparietal junction is implicated in many tasks of mentalizing.

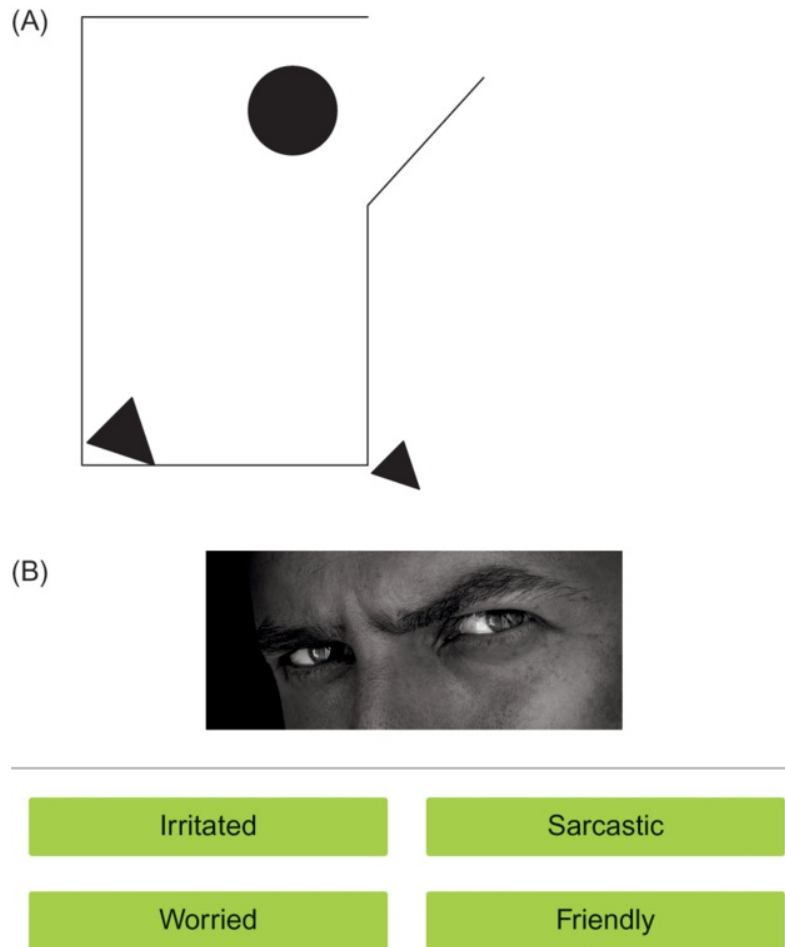


Figure 13.10 Tasks that involve mentalizing.

(A) In the famous Heider-Simmel illusion, people attribute goals and feelings to simple shapes that move around a box. (B) In the Mind-in-the-Eyes task, participants are asked to infer the person's mental state from a face image cropped to show only the eyes.

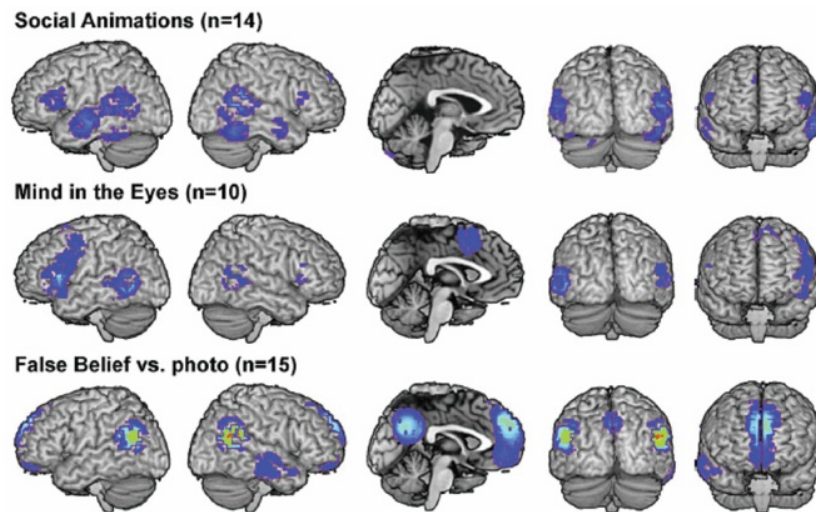


Figure 13.11 Brain activity during different tasks of mentalizing.

These figures illustrate the results of a meta-analysis of brain imaging studies using different tasks to assess mentalizing ability (Schurz et al., [2014](#)). The tasks – social animation, Mind-in-the-Eyes, and false belief tasks – are more fully described in the text. All three types of task activate the temporoparietal junction, whereas inferior frontal cortex is activated most strongly by social animations and mind-in-the-eyes tasks, and medial prefrontal cortex is most strongly activated by false belief tasks.

Another task used to study mentalizing is referred to as the Mind-in-the-Eyes task. In this task, participants view pictures of eyes cropped out of a face, and must decide what emotion the person is feeling ([Figure 13.10B](#)). fMRI studies have contrasted brain activity when making such emotional-state attributions about others with brain activity when making nonmentalizing judgments, such as determining the person's gender (e.g., Baron-Cohen et al., [1999](#)). Generally speaking, such studies have found that inferring an emotional state based on the eyes is associated with increases in activity in the left frontal lobe, including inferior frontal cortex, as well as temporoparietal junction ([Figure 13.11](#); Schurz et al., [2014](#)).

Finally, another set of studies has examined neural activity during reasoning about the false belief task. Studies have typically compared false belief reasoning with a nonsocial control condition, such as reasoning about the presence of a hidden physical process, for example, melting or rusting (e.g., Saxe and Kanwisher, [2003](#)). Across a

number of similar studies, the common areas activated by false belief reasoning included temporoparietal junction, medial frontal cortex, and precuneus ([Figure 13.11](#); Schurz et al., [2014](#)).

Across these different mentalizing tasks, we see both similarities and differences in the mental processes that are likely involved as well as in the brain regions that are activated. For example, although all the tasks attempt to tap the process of inferring mental states, they differ in the visual complexity of the stimulus (e.g., moving versus static, face versus simple shapes) and the degree to which higher-level reasoning is involved (e.g., reasoning about hidden or counterfactual situations, as in the false belief task). Examining the pattern across all tasks in [Figure 13.11](#), we see that one area commonly activated is the temporoparietal junction, implying that this region supports mentalizing across a wide range of tasks.

Although evidence is strong that the temporoparietal junction is important in theory-of-mind tasks, less clear in our current state of knowledge is why this region is important and exactly how it supports mentalizing inferences. For example, perhaps its proximity to superior temporal regions that code for biological motion is critical, given that the motions of other people (e.g., eye movements, gestures) give us clues to their mental states. Alternatively, perhaps the proximity of the temporoparietal junction to parietal regions involved in attentional orienting is key, if attention is needed to bind together different cues that support mental attributions. One theory proposes that the temporoparietal junction represents a unique anatomical nexus in which processing of attention, memory, and language come together to support social cognition (Carter and Huettel, [2013](#)). Closer analysis also reveals that the general region referred to as the temporoparietal junction includes smaller subregions that may play different roles. For example, in [Figure 13.11](#) we can see that the temporoparietal activation for false belief reasoning is somewhat more dorsal and posterior compared to the activation for the social animacy and Mind-in-the-Eyes tasks.

Beyond the temporoparietal junction, other regions are activated consistently for one kind of mentalizing task but not for others. For example, lateral inferior frontal cortex is

more strongly implicated in the social animacy judgments (Heider–Simmel illusion) and Mind-in-the-Eyes tasks, compared to the false belief tasks. Considering what we learned about the role of inferior frontal cortex in imitation, it seems plausible that this region is activated in mentalizing tasks that could involve some motor mimicry (e.g., mimicking movements in social animacy tasks or facial expressions in the Mind-in-Eyes task) but not in those that are more abstractly cognitive, such as the false belief task. On the other hand, activity in the medial prefrontal cortex is more strongly implicated in false belief reasoning tasks than in the other mentalizing tasks, perhaps due to the cognitive complexity involved in false belief reasoning. In summary, although the temporoparietal junction is clearly a crucial element of “the social brain,” lateral inferior frontal cortex and medial prefrontal cortex are also consistently involved in certain mentalizing tasks.

Empathy

Both the imitation and theory-of-mind concepts attempt to explain how we understand the mental states of other people. But how do they relate to the concept of empathy? Does understanding other people’s actions, feelings, intentions, or beliefs mean that we empathize with them more? Part of the challenge in addressing this question involves the thorny concept of [empathy](#) itself. Indeed, though empathy is commonly defined as the ability to understand how another person feels, much ink has been spilled parsing what this term really means (see Batson, [2009](#); Walter, [2012](#); Zaki and Ochsner, [2012](#), for reviews).

One useful way of thinking about empathy is to distinguish among three main components or facets, as explained more below: (1) emotional contagion that causes us to feel as others feel; (2) cognitive perspective-taking that allows us to understand another person’s point of view; and (3) pro-social action, which involves behavior targeted to help another person in need. This latter component underscores that we typically use the term “empathy” to describe situations in which another person has a

need for help. That is, we usually speak of empathy for people in pain or distress, rather than empathy for people feeling joy, pride, or happiness, even though those latter mental states are certainly ones that we can understand in others.

To illustrate these three facets of empathy, imagine that you see a small child fall from the monkey bars at the playground and begin to cry. The emotional contagion aspect of empathy would result in you feeling distressed, as the child does. The cognitive perspective-taking component could include both a cognitive understanding that the child is hurt, and also an understanding that the child probably wants his parents. The pro-social aspect of empathy would involve behavior to intervene on behalf of the child, such as rushing to give aid to the child, or locating his parents. In our everyday use of the term “empathy,” we may be loosely referring to any or all of these components. However, to understand empathy from a research perspective, it can be useful to separate them.

Given what we have discussed in the previous sections, you can probably see connections between the concept of simulation (or imitation) and the emotional contagion component of empathy. That is, neural mirroring of another person’s emotional state seems like a plausible mechanism of emotional contagion. Imitation and emotional contagion are not synonymous, because not all imitative actions are emotional. For example, imitating your tennis teacher’s serve would not qualify as emotive or empathic. However, feeling sad when you see another person’s sad expression would qualify as emotional contagion and could be explained through imitation or mirroring of that person’s sad state.

The emotional contagion aspect of empathy can even be modeled in less cognitively complex species such as mice (Panksepp and Panksepp, [2013](#)). For example, one study found that mice who are cage mates seem to mirror one another’s pain (Langford et al., [2006](#)). Specifically, mice showed exaggerated pain behavior in response to a painful stimulus when they observed their cage mate also experiencing pain, compared to when they were observed alone or in the presence of a stranger mouse experiencing pain. This

seems to suggest a kind of contagion for pain (and one that depends on the social relationship between the mice). However, we would not necessarily conclude from such findings that the mouse appreciates the other mouse's point of view (cognitive perspective-taking).

Just as imitation relates to the concept of emotional contagion, you can consider how the theory-of-mind concept that we addressed earlier relates to the cognitive perspective-taking component of empathy. In both cases, the emphasis is on higher-level cognitive representations of the mental states of another, not mere mimicry or mirroring. In the case of cognitive perspective-taking as a component of empathy, we are generally focused on situations that involve pain or distress, not unemotional knowledge states. For example, understanding that Sally will look in the wrong place for the marbles in the false belief task requires theory of mind, but we wouldn't necessarily call it empathetic. On the other hand, if Sally angrily hurled the basket across the room because she didn't find the marbles, we have a cognitive understanding that she is frustrated because the marbles weren't where she expected them to be. In this way, cognitive perspective-taking can lead us to empathize with Sally's emotional state, extending beyond a mere "mirroring" of her angry expressions toward a deeper understanding of why she is behaving angrily.

Studies suggest that systems for both simulation and mentalizing are involved in formulating an accurate understanding of other people's emotions. For example, in one study, participants were videotaped telling autobiographical stories about themselves (Zaki et al., [2009](#)). They later rated their own emotions during the videos. A second group of participants then watched the videos, while fMRI scans were being taken, and were asked to evaluate the emotional states of the people in the videos (see [Figure 13.12](#)). Researchers could then quantify how well the viewer's estimation of the emotional state of the person in the video matched the person's own rating, in order to quantify "empathic accuracy." Across participants, those with greater empathic accuracy tended to show greater activity in some regions associated with mirroring

(e.g., inferior parietal lobe) as well as some regions associated with mentalizing (such as medial prefrontal cortex). However, activity in other regions implicated in mirroring (e.g., inferior frontal cortex) and mentalizing (e.g., temporoparietal junction) did not correlate with empathic accuracy, raising questions about exactly what role they play in empathy.

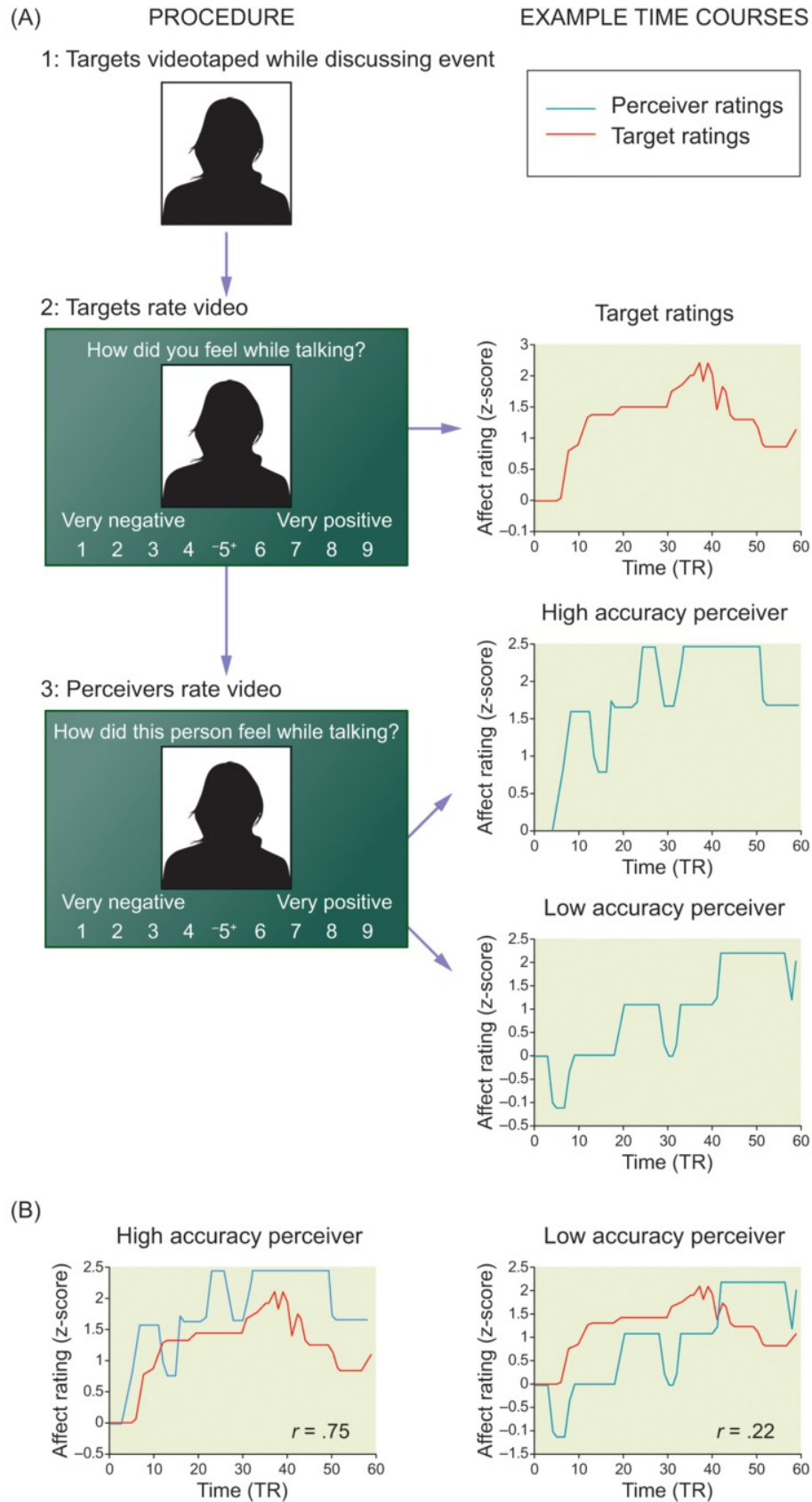


Figure 13.12 Task used to measure empathic accuracy.

Researchers videotaped one set of participants (the targets) telling autobiographical stories, and then had them rate their emotions during the telling. A second group of participants (the receivers) then watched the videos and also made ratings of the target's emotions during the videos. Receivers with high empathic accuracy were defined as those whose ratings correlated highly with the rating of the original target. In the figure, accuracy is defined by the match between the lines for the target (red line) and the receiver (blue line).

(from Zaki et al., [2009](#))

Other studies suggest that social relationships may affect the degree to which we engage “mirroring” versus “mentalizing” brain regions in situations that seem to call for empathy. For example, in one study, participants viewed either a friend or a stranger experiencing social exclusion (Meyer et al., [2013](#); see In Focus feature for more about the study of social exclusion). Participants were more likely to activate their own neural pain regions when viewing a friend being excluded (apparently “mirroring” the friend's pain), whereas they were more likely to activate “mentalizing,” or cognitive perspective-taking regions, such as medial frontal cortex, when viewing social exclusion of a stranger. These results suggest that unraveling how these different networks contribute to empathy may depend on examining contextual factors such as the social relationships between the people being studied.

Finally, what do we know about the third component of empathy, that is pro-social behavior? Does helping behavior automatically arise when emotional contagion or cognitive perspective-taking tells us that someone else is in need? Do we always take action to help the child who fell in the playground, or to kindly explain to a frustrated Sally where her marbles can be found? You probably know from your own experience that, sadly, pro-social action does not always follow from a perception that others are in need. In extreme cases, sadistic or despotic people may actually use their understanding of others' feelings or needs for antisocial ends. Thus, for a full understanding of empathy, ultimately we need to appreciate not only how the feelings of others are

represented in our own brains, but also how our understanding of those feelings translates into pro-social action.

Cognitive neuroscientists have generally spent more time researching the neural basis of imitation and theory of mind than the neural basis of pro-social behavior, leaving this third component of empathy less well understood, at least in neural terms (Zaki and Ochsner, [2012](#)). Partly this may be because helping behavior is harder to study in the lab settings in which cognitive neuroscience studies usually take place. However, in recent years, several studies have attempted to connect neuroscience findings with pro-social behavior outside the lab.

For example, in one study, participants completed a daily diary of helping behavior over a period of two weeks, each day noting the number of times they engaged in specific behaviors such as giving a friend a ride or holding a door open for a stranger (Rameson et al., [2012](#)). Later, the same participants completed an fMRI study in which they viewed pictures of people in sad situations. Those who reported more daily helping behavior toward friends tended to show greater activation of medial prefrontal cortex during the empathy-inducing fMRI task. Interestingly, though, daily helping of strangers was not correlated with any of the neural measures. Once again, we see that neural mechanisms associated with empathy appear to depend on preexisting social relationships (i.e., friend versus stranger).

Returning to the big picture, it is useful to consider why empathy, or more generally, the understanding of other minds, evolved (see Gonzalez-Liencre et al., [2013](#); Panksepp and Panksepp, [2013](#)). One possibility is that understanding other people leads us to be better able to predict their actions. When environments are predictable, we can better adapt our behavior; and when living in a social group, an important aspect of the environment is the social group. How better to predict that environment than to make inferences about the behavioral inclinations of others?

Another possibility, not mutually exclusive with the first, is that empathy leads to pro-social (helping) acts that are necessary for functional group living. Pro-sociality may have originated in systems of parental care in mammals, in which understanding the

emotions and needs of offspring is crucial for their survival, and from there developed into even more sophisticated forms of social bonding among group members who depend upon one another. The tendency for empathy to be differentially directed toward offspring or social in-group members points directly to the need to better understand how we form concepts of our social in-groups and out-groups, an issue that we address in more detail in a later section.

Self Versus Other

While we are capable of empathy, including feeling other people's pain and distress, we are also fully capable of distinguishing our feelings from those of others. For example, if you beat your friend in a race, you can understand simultaneously that you feel proud of your win and that your friend feels disappointed. Likewise, even though social influence has the potential to sway all of our judgments and beliefs in accordance with the views of our friends, we are still capable of distinguishing our own beliefs and those of others. For example, because you possess theory of mind, you can comprehend that your friend has conservative political beliefs while you have liberal political beliefs, much as you can comprehend that Sally believes that the marbles are in the basket even though you know that they have been moved. These examples illustrate that we have knowledge about ourselves as well as about others. Further, they raise questions about whether similar systems are used to represent reflections about our own mental states as well as reflections about those of others.

Just as we can mentalize about others, so too can we make mental-state attributions about ourselves, for example, reflecting upon our own goals, intentions, feelings, beliefs, traits, and judgments. Perhaps not surprisingly, when we engage in mentalizing about the self, some similar regions are activated as when we mentalize about others, suggesting a common basis for mental-state attribution (e.g., Wagner et al., [2012](#)). For example, a meta-analysis found that judgments about the self (e.g., trait judgments such as "I get angry easily") as well as judgments about others (e.g., "My best friend gets

angry easily”) activated regions associated with mentalizing that we learned about in previous sections, including left temporoparietal junction (TPJ) and medial prefrontal cortex (mPFC; [Figure 13.13a](#); Denny et al., [2012](#)).

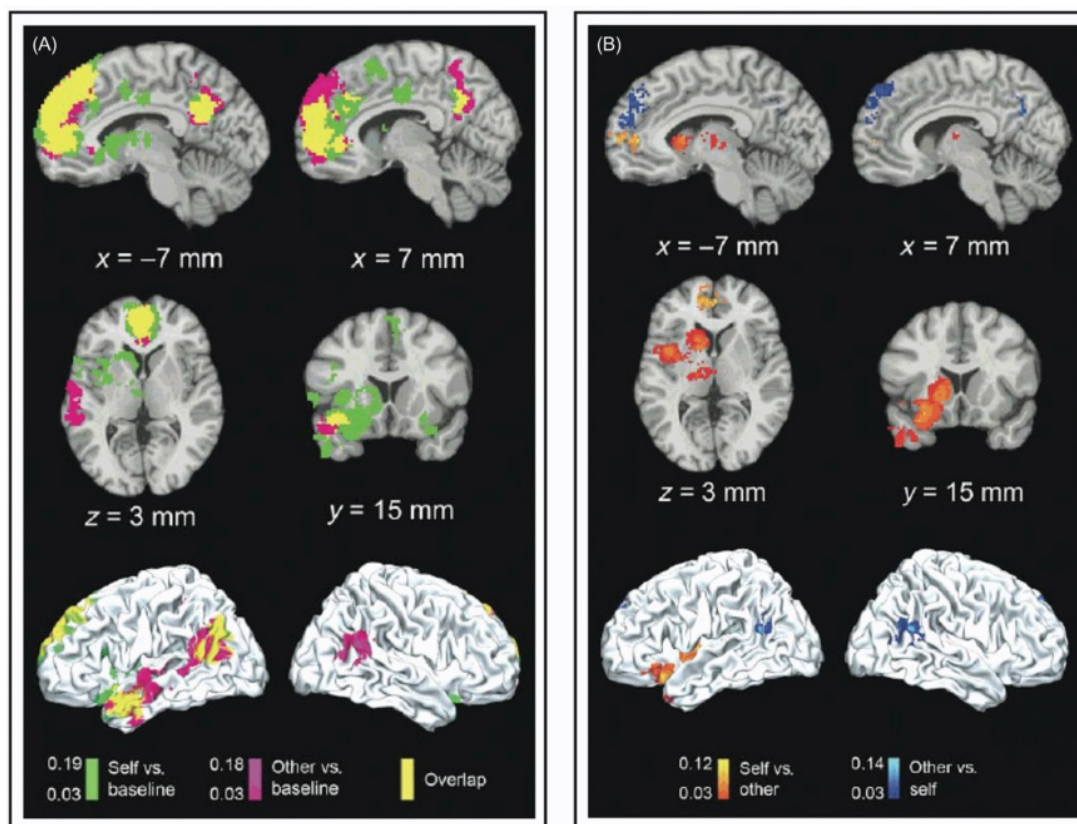


Figure 13.13 Comparison of brain regions activated when making judgments about the self versus judgments about other people.

(A) Mental-state attributions about the self and about others activate overlapping networks, including medial prefrontal cortex and left temporoparietal junction. (B) When directly compared with one another, self- and other-judgments showed distinct patterns. Specifically, self-judgments led to greater activation in ventromedial and ventrolateral prefrontal cortex, whereas other judgments led to greater activation in dorsal-medial prefrontal cortex and temporoparietal junction.

(from Denny et al., [2012](#))

Interestingly, another region that we previously discussed as relevant to mentalizing, namely, inferior frontal cortex, was not particularly activated during these mental-state

attributions. Perhaps this is because the task – i.e., judging whether “I get angry easily” or “She gets angry easily” – involves higher-level cognitive judgments, rather than imitative actions, which are more closely tied to inferior frontal activity.

The meta-analysis also revealed distinctions between regions activated by self-judgments and other-judgments (Denny et al., [2012](#)). In direct statistical comparisons between the two, judgments about the self activated a more ventral portion of mPFC as well as ventrolateral prefrontal cortex to a greater degree than judgments about others. Conversely, judgments about others activated a more dorsal portion of the mPFC as well as TPJ to a greater degree than self-judgments ([Figure 13.13b](#)). Thus, even though the two types of judgments activate overlapping mentalizing regions, neural activity is able to distinguish self from others.

Interpreting neural differences between judgments about the self and judgments about others can be challenging because of certain confounds that are often present in the comparison. Familiarity is one such confound: obviously we are all more familiar with ourselves than we are with other people. As a result of that familiarity, we have greater depth of knowledge about the self, and virtually all that knowledge comes from direct experience. Another potential confound has to do with specificity. For example, the best-controlled studies compared judgments about the self with judgments about a specific other person (e.g., one’s best friend, or a specific famous person) rather than judgments about other people or groups in general. We may also tend to view the self more favorably than we view others, and we may have more emotional attachments to the self, introducing possible emotional confounds into the comparison. In addition, social psychologists have long described a phenomenon known as the [fundamental attribution error](#), in which people tend to see their own actions as more socially constrained yet assume the actions of others are more attributable to their inherent personalities (Ross, [1977](#); see also Moran et al., [2014](#)). Any one of these differences between self-perception and other-perception could potentially account for distinct

patterns of neural activity when reflecting upon the self versus others (for additional critiques, see Gillihan and Farah, [2005](#)).

Another way that judgments about the self differ from judgments about others is in their temporal perspective. That is, when we think about our own mental states, we are often drawing upon the present moment, whereas when we think about others, we are often drawing upon stored memories from past encounters. Interestingly, when we are prompted to think about ourselves in the past or future, we may be more likely to call upon processes that we use to think about other people. One neuroimaging study asked college students to indicate whether various adjectives described themselves in the past (“Five years ago, I was”), in the present (“At present, I am”), and in the future (“In five years, I will be”), and compared each condition to a baseline in which adjectives were categorized as positive or negative (D’Argembeau et al., [2010](#)). Self-related judgments activated mPFC more strongly for judgments of the present self, compared to either the past or future self (which did not differ). Indeed, other studies have found that judgments about future or past selves tend to produce mPFC activation that more closely resembles the activation produced when thinking about others (D’Argembeau et al., [2008](#); Ersner-Hershfield et al., [2009](#)). This research underscores the importance of the present-moment perspective in driving mPFC activity during self-judgments.

The difference in neural response between reflecting about the mental states of the self versus others can also be reduced by increasing the closeness of the relationship with the other person. In other words, the mPFC activity between self-judgments and other-judgments is more similar when the other being judged is someone in a close relationship with the self (such as a best friend), rather than someone more interpersonally distant (e.g., Krienen et al., [2010](#)). This finding – that greater social closeness is associated with greater self-other overlap in neural activity – fits very well with research on empathy, in that we generally show greater empathy toward those with whom we share close relationships.

Taken together, all of these findings suggest several conclusions about mentalizing about the self: first, thinking about our own mental states calls upon similar, but not identical, brain regions as thinking about the mental states of others. Second, the degree of similarity between mPFC activation while mentalizing about the self versus others can be predicted by factors such as the temporal perspective (whether judging past, present, or future self) and the closeness of the relationship with the other person being judged.

Autism and Social Cognition

As with any aspect of cognition, one way to better understand the processes involved in social cognition is to examine clinical conditions in which those processes appear to go awry. Examining clinical conditions can help us to identify areas of deficit and possible intervention for the patients themselves, and it can also provide a perspective on the elements that constitute typical cognitive processing. Although there are a number of clinical conditions in which social functioning is affected, by far the most relevant to understanding social cognition is autism. Autism will be discussed more generally in [Chapter 15](#) in the context of other developmental disorders, but here we focus specifically on the aspects of autism that are most relevant to social cognition.

According to the most recent diagnostic criteria in the DSM-5 (American Psychiatric Association, [2013](#)), a diagnosis of [autism spectrum disorder](#) depends on the presence of two main characteristics: (1) impairment in social interaction across a range of contexts, such as deficits in social reciprocity, nonverbal communicative behavior, or development of social relationships; (2) restrictive or repetitive activities or interests, including repetitive motor actions (stereotypies such as hand-flapping), fixated narrow interests (such as an obsession with baseball statistics or an absorption with mechanical movement, like the spinning of an electric fan), inflexibility in the face of changes in routine, and/or hyper- or hyposensitivity to sensory information in the environment. In addition, in order to meet diagnostic criteria, the symptoms must be

present in some form in early development, must result in significant impairment in social, school, or work settings, and must not be better accounted for by global intellectual delay (such as mental retardation). Clinicians rate the level of severity of these symptoms and can specify whether or not the diagnosis also includes significant language impairment.

It's important to appreciate that the diagnostic criteria for autism have been in flux in recent years, and that research in the past may have been conducted with participants with slightly different profiles or diagnostic labels (e.g., Kent et al., [2013](#); Kulage et al., [2014](#); Tsai and Ghaziuddin, [2014](#)). For example, you have probably heard the term Asperger syndrome, which was a separate diagnosis in earlier versions of the DSM but is now folded under the single umbrella diagnosis of autism spectrum disorders. [Asperger syndrome](#) describes individuals who meet the criteria for autism but are high-functioning in terms of their overall intelligence and language skills. Temple Grandin, whom we met in the vignette at the beginning of the chapter, is one such example. As with all clinical conditions, we must appreciate that diagnostic definitions are works in progress, not set in stone, and that definitions are likely to change again in the future as knowledge increases. Moreover, there is variability within any diagnostic category, meaning that not all individuals within a category think or behave alike in all ways. However, even with these ambiguities in mind, there is no question that social impairments lie at the core of autism.

Autistic children have profound social deficits that are not observed in typically developing children or in those with other forms of developmental disorder. For example, children with mental retardation seek interaction with adults, smile, and appreciate being held when hurt. Autistic children, on the other hand, may prefer to engage in routinized robotic behavior. They may scream if approached, as if being intruded upon too closely, and often avoid making eye contact with other people. They appear indifferent to the presence of people, acting as if other people are pieces of furniture or “looking through” them as if they didn't exist. Moreover, they tend to perform best on cognitive tasks that do not require human interaction. For example, on

recognition tests, they often can identify inanimate objects, such as a screwdriver, more readily than objects representing something human, such as a face.

Because autism is characterized by social deficits, naturally many autism researchers have examined brain systems that participate in social cognition. Some have proposed that the mirror neuron system may not be operating normally in autism, a theory sometimes referred to as the “broken mirror theory” of autism (Iacoboni and Dapretto, [2006](#); Oberman and Ramachandran, [2007](#)). For example, in a task that required participants to imitate facial expressions of emotion, autistic participants did not activate the premotor regions as extensively as did control participants ([Figure 13.14](#)), adding credence to the idea that this neural system may be deficient in autism (Dapretto et al., [2006](#)).

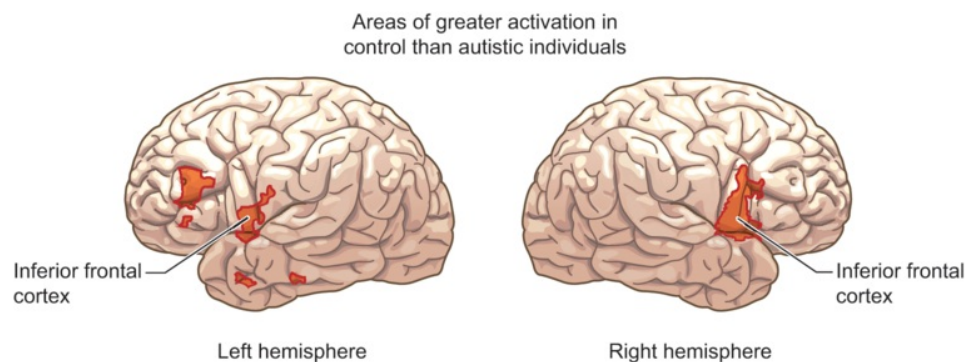


Figure 13.14 Brain activation differs between control participants and autistic participants during an imitation task.

The task required participants to imitate facial expressions of emotion. Regions highlighted, including inferior frontal cortex, showed greater activity for the control than autistic participants.

(from Dapretto et al., [2006](#))

However, because autistic children are able to correctly imitate goal-directed hand motions (Hamilton et al., [2007](#)), it is not clear whether global difficulties in motor mirroring constitute a core deficit in autism. A meta-analysis integrating the results of 25 studies concluded that deficits in the response of the mirror neuron system in autism seem to be limited to the imitation of facial expressions or other emotional gestures,

with less evidence that nonemotional actions, such as imitative hand movements, are affected (Hamilton, [2013](#); see also Kana et al., [2011](#)).

Some researchers have speculated that social deficits in autism may originate from difficulties perceiving and recognizing emotional expressions in others. Autistic people look at faces differently, fixating less on the eyes than do neurologically intact people (e.g., Klin et al., [2002](#); Spezio et al., [2007](#)). These findings are consistent with clinical reports that autistic people tend not to make eye contact with others. Imaging studies have shown that people with autism do not engage the normal face processing neural machinery when presented with pictures of faces. For example, when viewing face images, activity in both the amygdala and the fusiform face area is lower in autistic people compared to neurologically intact people (e.g., Ashwin et al., [2007](#); Pierce et al., [2001](#)).

Moreover, people with autism ignore specific cues from faces that are especially useful for social interaction, such as gaze direction. In one study, participants viewed faces in which the eyes were either appropriately looking toward the location of a checkerboard or gazing off in a different direction (Pelphrey et al., [2005](#)). Nonautistic participants showed a pattern of brain activity in the superior temporal sulcus that was sensitive to the gaze direction, but autistic participants did not (see [Figure 13.15](#)). Similarly, another study found that adults with autism showed less activity in response to direct gaze versus averted gaze in regions such as medial prefrontal cortex, temporoparietal junction, and superior temporal sulcus, whereas controls showed more activity in these regions in response to direct versus averted gaze (von dem Hagen et al., [2014](#)). While most of these studies focused on faces, other studies indicate that difficulty in engaging the neural systems for processing social cues extends to the auditory domain. For example, autistic people exhibited a lower temporal lobe response to voices of people, compared to the response in neurologically intact people, whereas the groups did not differ in their responses to nonvocal sounds (Gervais et al., [2004](#)).

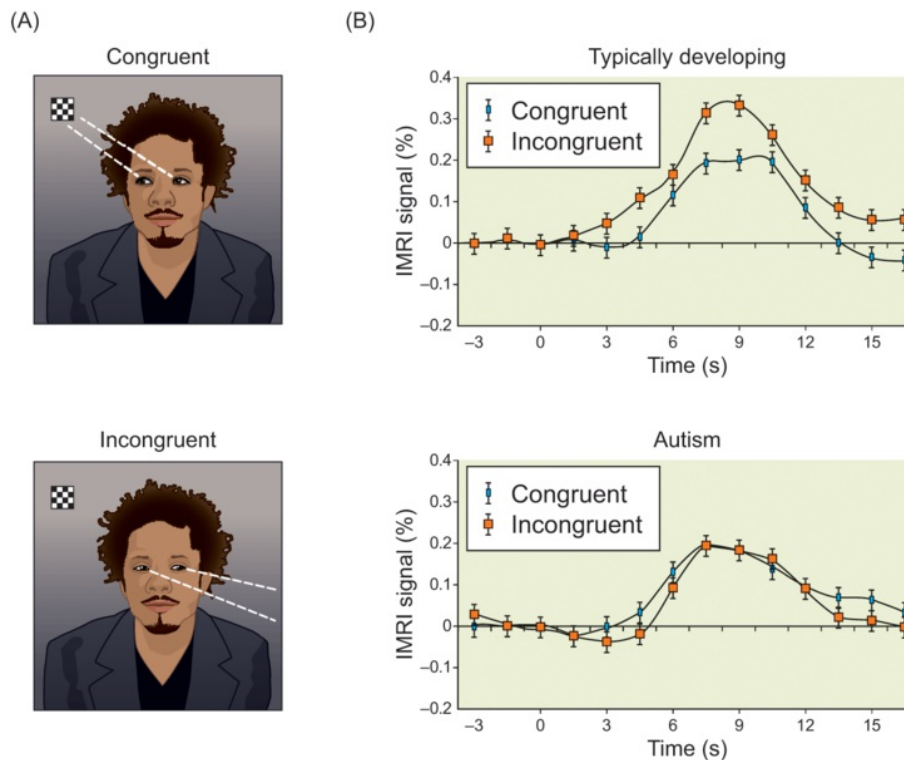


Figure 13.15 A task sensitive to gaze direction activates superior temporal sulcus in control participants but not autistic participants.

(A) Participants viewed a face whose eyes were either looking toward a target stimulus (congruent gaze) or toward an empty location (incongruent gaze). (B) Activity in the right superior temporal sulcus was sensitive to gaze direction in the typically developing (control) participants (top) but not the autistic participants bottom.

(Pelphrey et al., [2005](#))

Other studies have addressed mentalizing abilities in people with autism. For example, individuals with autism have difficulty explaining why characters in vignettes act the way they do, and they have difficulty with false belief tasks (e.g., Baron-Cohen et al., [1985](#); White et al., [2009](#)). Generally, when attempting to understand the viewpoint or motivations of others, autistic people do not tend to activate the brain regions that neurologically intact individuals do (Zilbovicius et al., [2006](#)). In one study, participants viewed the movement of shapes that followed either a random pattern or a pattern that suggested that the shapes were intentionally interacting with one another, as in the

Heider–Simmel illusion discussed earlier (Castelli, Frith, Happé, and Frith, [2002](#)). Compared to control participants, autistic participants showed less activity in medial prefrontal cortex and temporoparietal junction during the Heider–Simmel movement condition. These results reinforce the idea that brain areas involved in mentalizing are not activated normally in autistic individuals.

Given that both neural mirroring and mentalizing (cognitive perspective-taking) are posited to contribute to empathy, one intriguing question is whether individuals with autism are capable of feeling empathy. Although debates persist in the literature, it appears that people with autism are capable of feeling “emotional empathy” – feeling what others feel, analogous to the emotional contagion discussed earlier – but they struggle more with “cognitive empathy,” or the cognitive inferences required to represent the feeling states of others (Blair, [2005](#)). For example, when viewing pictures of people in pain, both control participants and adults with autism activated the brain regions thought to be involved in the vicarious experience of pain (Hadjikhani et al., [2014](#)). Likewise, on self-report measures, boys with autism indicated levels of compassion toward victims (caring about people who were hurt) that was indistinguishable from those of control participants (Jones et al., [2010](#); see also Deschamps et al., [2014](#); Rogers et al., [2007](#)). Other research has found that adults with Asperger syndrome have difficulty in inferring the emotional state of a person depicted in a picture, but show normal empathic emotional reactions once they are told what emotion the picture portrays, such as reporting more concern for people labeled as more sad (Dziobek et al., [2008](#)).

This dissociation between emotional and cognitive empathy can help us to appreciate how Temple Grandin could design humane facilities for cattle based on her understanding of the cows’ needs and feelings, while at the same time struggling to cognitively comprehend the more complex emotional states of fellow humans. Beyond helping us to understand the capacities of people with autism, the results pertaining to

empathy help to delineate different forms of empathy within typically developing people as well.

In Focus: The Pain of Rejection

Scientists have spent years elucidating the neural underpinnings of physical pain, but recently affective neuroscientists have considered the underpinnings of social pain (see MacDonald and Leary, [2005](#), for a review). Does the pain of rejection “hurt” in the same places in the brain that physical pain does?

One influential study suggested that it does (Eisenberger et al., [2003](#)). In this study, participants played a virtual ball-tossing game with two other participants, depicted as cartoon characters on a computer screen. Actually, the other “participants” were just a rigged computer program. First the participant watched the two others toss the virtual ball back and forth. Then, the participant was drawn into the game, and all three players tossed the ball around. In the third portion of the game, suddenly the other two “players” stopped tossing the ball to the participant. Not surprisingly, participants tended to say that they felt ignored and excluded. At the same time, they showed increased activity in the anterior cingulate cortex and right ventrolateral prefrontal cortex compared to earlier when they had been participating in tossing the ball. Because the anterior cingulate is also activated by physical pain, these results could be interpreted as indicating that social exclusion “hurts” because it activates the same area in the brain as does physical pain.

However, as other researchers pointed out, the exclusion condition probably differed from the inclusion condition in another way: namely, that the exclusion condition violated expectations (Somerville et al., [2006](#)). That is, the participant was probably surprised when the others stopped throwing the ball to him or her. Was the cingulate cortex activated because of the perceived social pain, or simply because of the violated expectation? Other studies have shown that the

cingulate cortex is activated by unexpected outcomes and other cognitive conflicts even in situations that do not involve pain of any sort (see [Chapter 11](#)). To differentiate between these two possibilities, Somerville and colleagues developed an experiment that included two different kinds of conditions: one that involved a violation of expectations and another that involved social feedback (indicating whether another “participant” reported liking the actual participant or not). They found that social rejection activated a different region of the cingulate cortex than did expectancy violation, indicating that these two processes are not one and the same, but rather are separable.

Additional research calls into question whether social rejection and physical pain actually share the same neural locus. One study examined neural activity on a more fine-grained level when participants experienced painful heat (compared to nonpainful warmth) and when they viewed pictures of their ex-partners (compared to pictures of friends; Woo et al., [2014](#)). Although participants rated the heat stimuli and the pictures of a previous romantic partner who had shunned them to be equally “painful,” distinct and nonoverlapping patterns of activity within the cingulate cortex and other brain regions were associated with each of these stimuli.

In addition to suggesting that the brain can, indeed, distinguish between different kinds of pain, the Woo et al. ([2014](#)) study reminds us of the challenges in addressing claims about whether the “same” region is activated in two different conditions. Using traditional analysis methods, the study found that a similar region of cingulate cortex was activated for physical and emotional pain. However, using a multi-voxel approach (see [Chapter 3](#)), the researchers observed that the pattern of activity across voxels in that commonly activated region differed between the two conditions, suggesting that the way the ACC processes physical and emotional pain is distinct. The neural patterns could be used with a high degree of accuracy to predict, in another set of people, whether

any given person was feeling physical pain or feeling emotional pain. Perhaps one day, your pattern of brain activity will provide a measure of how heartbroken you really are!

Perceiving and Judging Social Groups

Are you part of the “in-crowd”? What is the “in-crowd,” anyway? An indisputable aspect of human social life is that we tend to form into groups. Social groups can be defined by many characteristics, and we all belong to more than one group depending on the circumstances. For example, in different circumstances you could think of your group as your relatives, people in your neighborhood, people sharing your religion, people sharing your race or ethnicity, people sharing your gender or sexual orientation, people attending your university, people sharing your nationality, or people sharing your favorite activities, such as those playing on your sports team or singing in your choir. The fact that we can belong to more than one group does not negate the fact that, when thinking about others, we often categorize them by their group membership. Furthermore, any concept of a social group implies that some people are in it and others are not.

One aspect of social cognition that has been studied for decades is the tendency to form stereotypes of social groups, particularly those to which we do not personally belong. In its most pernicious form, stereotyping can contribute to prejudice and discrimination against other people, particularly against minority out-groups. Why do people engage in stereotyping, prejudice, and discriminatory behavior, and what mechanisms sustain it? Clearly, dealing with the full scope of this problem would involve understanding behavior at the level of the group, inequalities in social structure and power, and how cultural norms and values are taught and learned. It would be naive to think that we can fully understand prejudice by looking deep within the brain. But can cognitive neuroscience contribute anything to knowledge in this important area? In the

following sections, we consider evidence from neuroscience studies of the cognitive processes involved in perceiving and making judgments about social groups.

In-group-Out-group Effects

One principle we have learned from cognitive neuroscience approaches is that the brain rapidly distinguishes between in-group and out-group categories. ERP methodology is especially well suited to determining the speed of categorizing stimuli, due to its high temporal resolution. Across a series of studies using ERP methods, it appears that within about a quarter of a second, people's brains are already responding to differently to stimuli based on their social category (Ito, [2011](#)).

In one study, researchers measured ERPs in response to faces of different races (Ito et al., [2004](#)). Some early ERP peaks appeared to respond equally to all faces, regardless of their racial category. For example, the face-specific N170 peak, which occurs about 170 ms after the presentation of a face, was bigger for faces than for other pictures, but did not differ for faces of different races. However, at around 250 ms, the ERP response was larger in response to faces of racial in-group members than out-group members. Early research was limited to white participants, but subsequent studies confirmed the same basic pattern – early neural differentiation of in-group and out-group – in both white and black participants (Dickter and Bartholow, [2007](#)). ERP research also reveals different responses to male versus female faces within about 200 ms, again implying that this aspect of social categorization is quickly distinguished (Ito, [2011](#)).

Although these studies have focused on social groups based on race and gender – highly salient social categories in many societies – social psychologists have long known that in-groups and out-groups can be formed very easily based on virtually any kind of distinction between people. When people are randomly assigned to groups, even through a coin toss, they later show evidence of favoring their own group (Tajfel, [1970](#)). This is a phenomenon that social psychologists refer to as “minimal groups,” meaning

that people can form into groups based on the most seemingly trivial of differences. In the most basic sense, the minimal-groups phenomenon underscores the fundamental human tendency to categorize others into in-groups and out-groups.

Using minimal-groups experiments, researchers have shown that even the simplest kinds of social categorization, established within a single experimental session, can affect how the brain responds to other people. For example, one study examined the N170 ERP response to faces of in-group and out-group members in a minimal-groups design (Ratner and Amodio, [2013](#)). Each participant first had to estimate the number of dots in various patterns, and then was given bogus information that he or she was either an “underestimator” or an “overestimator.” Then the participant viewed faces of other people who were labeled as underestimators or overestimators. Researchers found enhanced N170 peaks (which occur less than two-tenths of a second after the image onset) when participants viewed faces of people belonging to the same fictitious group as themselves (see [Figure 13.16](#)).

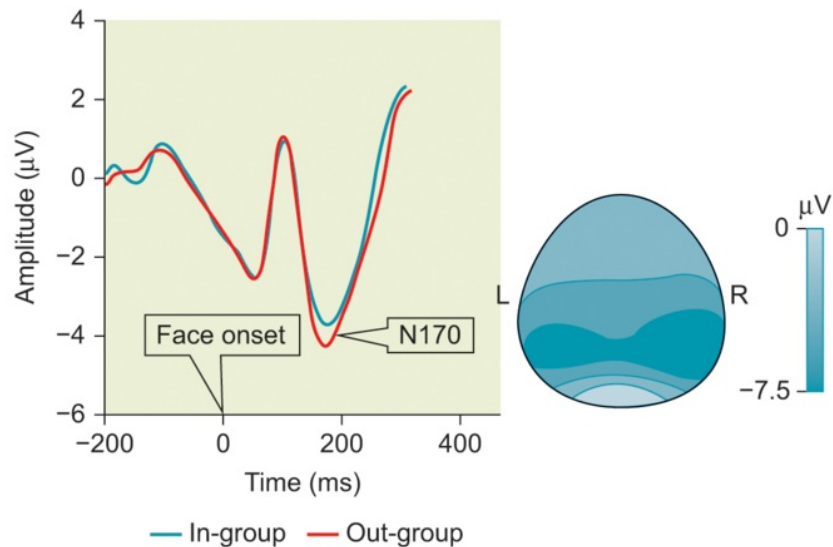


Figure 13.16 The brain differentiates between in-group and out-group members, even when group membership is arbitrary.

Participants were randomly assigned to social groups by being designated as “underestimators” or “overestimators” based on a bogus dot estimation task. When later viewing faces of other people labeled as either under- or overestimators, people showed larger N170 responses (recorded over posterior scalp sites) to the faces in their own group.

(from Amodio, [2014](#))

In an fMRI study using a minimal-groups design, participants were randomly assigned to belong to either the “Leopards” or the “Tigers” team, and they were encouraged to learn which other participants belonged to their team versus the other team, supposedly for a later phase of the study (Van Bavel et al., [2008](#)). Brain imaging results showed increased activity in a number of regions, including amygdala, orbitofrontal cortex, and fusiform gyrus, when participants viewed their own team members versus members of the other team. Moreover, the difference in orbitofrontal cortex activity in response to own-team versus other-team faces predicted how much the participants favored their own team members in subsequent ratings of the likability of each face. As with other minimal-groups designs, the difference between the neural responses to in-groups versus out-groups could not be accounted for by prior

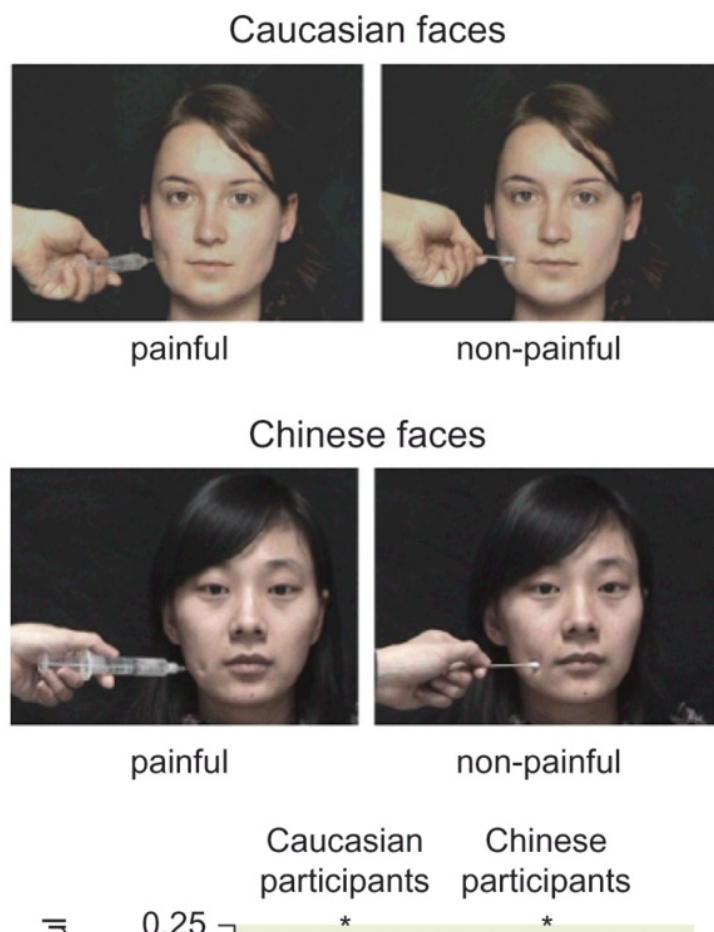
experience with the group, because the participants did not know each other before the study and the groups were entirely fictitious.

Although it is interesting to know that even minimally defined group membership can affect the brain's response to other people, it is also reasonable to ask whether some kinds of group membership are more salient than others. For example, consider a social category such as race, which is likely to be deeply entrenched due to sociocultural learning. Is race-based categorization ignored when other social categories, such as minimally defined social groups, are emphasized by an experiment? In one study, white participants were randomly assigned to either the "Leopards" or "Tigers" team, and then viewed faces and had to learn to which team they belonged (Ratner et al., [2013](#)). Half of the "Leopards" faces were white and half were black, and likewise for the Tigers. Then, in a later step, participants viewed the faces again and had to indicate the associated team, while fMRI scans were taken. Multivariate pattern analysis of the fMRI data – which is sensitive to subtle differences in activity across a pattern of voxels within a particular brain region– found evidence of different patterns of activity in fusiform gyrus while viewing black versus white faces, even though race was irrelevant to the task of deciding the team for each face. Results such as these suggest that some dimensions of social grouping, such as race, may be processed even when they are not relevant to the immediate social categorization task.

Not surprisingly, evidence suggests that we show greater empathic neural responses to those whom we perceive to be within our own social group. In a somewhat humorous example, fans of the rival Yankees and Red Sox baseball teams watched videos of baseball plays that favored either their team or the rival team (Cikara et al., [2011](#)). Yankees fans showed elevated activity in a caudal region of the anterior cingulate and in the insula (regions also activated by pain and disgust) when the Yankee players performed poorly or when their rival Red Sox players performed well, and they showed elevated activity in the reward-related ventral striatum when the Yankee players

performed well or Red Sox players performed poorly. Needless to say, the Red Sox fans showed the opposite pattern.

In more sobering results, other studies have found that empathic responses are more pronounced when we view people of our own racial group in distress, compared to people of other racial groups. For example, one study showed pictures of painful (needle) and nonpainful (Q-tip) stimulation of both Caucasian and Chinese faces to both Caucasian and Chinese participants (see [Figure 13.17](#); Xu et al., 2009). Caucasian participants showed greater activation of the anterior cingulate in response to painful stimulation of Caucasian compared to Chinese faces, and Chinese participants showed the opposite pattern. Other studies have found that the degree of insula activation in response to seeing an in-group member's pain can predict greater helping behavior (Hein et al., 2010). Such findings of greater in-group empathic responses lead us to consider not only the existence of social categories, but also how such categorization may lead toward biased behavior.



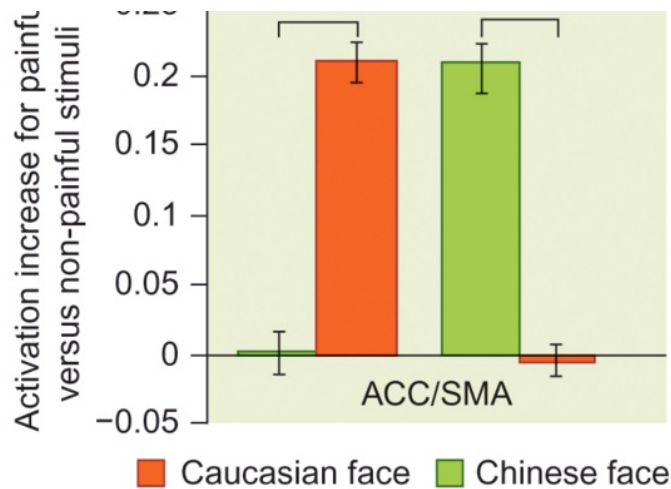


Figure 13.17 The brain's response to another person's pain depends on the person's social category.

Chinese and Caucasian participants viewed pictures (top row) of Caucasian and Chinese faces receiving either painful or nonpainful stimulation. Participants showed enhanced activity in the anterior cingulate/supplementary motor area (ACC/SMA) for painful versus nonpainful stimulation only when the face matched the participant's own social category.

(from Xu et al., [2009](#))

Stereotyping and Prejudice

The formation of social groups can be innocuous in some circumstances, but it can also lead to biased behavior in various forms. Biases in beliefs, attitudes, and behaviors are often discussed with reference to the concepts of stereotyping, prejudice, and discrimination. Traditionally, [stereotyping](#) refers to the tendency to assume that certain characteristics are universally true of group members. For example, we may hold a stereotype that women are nurturing or that Asians are good at math, meaning that we assume something about individuals within these groups simply based on group membership. We are more likely to hold stereotypes about groups to which we do not belong. [Prejudice](#), in turn, refers to a negative attitude about a particular social group. For example, imagine someone who expresses a general dislike for immigrants; he would be called prejudiced. [Discrimination](#), finally, refers to behavior that is biased

against a particular social group. For example, consider a company CEO who pays black workers less than white workers, or a restaurant manager who refuses to serve people with disabilities. Stereotyping, prejudice, and discrimination all involve biases about social groups, but they are distinguishable in the degree to which they are centrally cognitive, affective, or behavioral manifestations of bias.

An important feature of bias is that it can often be implicit, meaning that we are not always aware of it in ourselves (e.g., Nosek et al., [2011](#)). That is, we may report that we perceive and treat blacks and whites equally, for example, while actually harboring unconscious cognitive biases that reflect stereotypes and prejudiced attitudes. Here neuroscience measures may have something important to add: by studying neural markers related to implicit social biases, we may uncover clues to beliefs or attitudes that people are unwilling to admit or are not even consciously aware that they possess (for reviews, see Amodio, [2014](#); Kubota et al., [2012](#)).

Some research has suggested that unconscious racial bias is associated with processing by the amygdala, which, as we know from [Chapter 12](#), is implicated in fear and high-arousal emotional reactions. The amygdala is essential for fear conditioning, and people acquire a conditioned fear to other-race faces more quickly than to faces of their own race (Olsson et al., [2005](#); see also Golkar et al., [2015](#)). In a neuroimaging study, researchers found that unconscious racial bias was correlated with activity in the amygdala (Phelps et al., [2000](#)). Unconscious bias was measured using a behavioral method that quantifies the speed of association between pictures of other-race faces and negative words (compared to other-race faces and positive words). The researchers found that the higher the measure of unconscious racial bias, the more the amygdala, particularly on the left, became activated (see also Senholzi et al., [2015](#)). However, patients with amygdala damage still show unconscious racial biases (Phelps et al., [2003](#)), indicating that this brain structure is not solely responsible for sustaining racial prejudice.

Other research indicates that regions implicated in cognitive control are activated in situations of potential racial bias. Cognitive studies have shown a relationship between

executive control skills and racial bias. For example, people who perform well on traditional tasks of executive control, including working memory, inhibitory control, and task-switching ability, tend to show less implicit racial bias (Ito et al., [2015](#); see also Klauer et al., [2010](#); Payne, [2005](#)). Supporting the involvement of cognitive control structures, one neuroimaging study found that in a condition that allowed for top-down control of biases, the anterior cingulate cortex and dorsolateral prefrontal cortex were more activated in response to black versus white faces, but the same pattern was not evident in a brief-exposure condition with little opportunity for cognitive control (Cunningham et al., [2004](#)). Another study found increased activity in the anterior cingulate cortex and related regions when participants were given feedback indicating that their performance was prejudiced (Fourie et al., [2014](#)). Because these frontal regions are known to be crucial in implementing cognitive control across a wide range of cognitive performance tasks, their activation in these studies suggests that cognitive control processes are elicited when participants seek to control potentially prejudiced thoughts or behavior.

In this day and age, most people know that overt racial bias is socially unacceptable, and are uncomfortable with the thought that they might act or think in a racist way. One study focused on this phenomenon by studying people's responses to their own errors that might imply they harbored a racial bias (Amodio et al., [2004](#)). In this study, people had to quickly press a button to indicate whether a picture was a gun or a tool. Just before the picture, participants were primed with a picture of an African-American or Caucasian person. Overall, participants tend to be more likely to mistakenly press "gun" when primed with an African-American face than when primed with a Caucasian face, indicating an implicit bias associating African-Americans and guns. Researchers examined the error-related negativity (ERN) evoked when participants made errors in this task, and found that the ERN was significantly higher when participants made racially charged errors (e.g., mistakenly pressing the button for "gun" rather than "tool" when primed by an African-American face), compared to

errors that would not imply racial bias (see [Figure 13.18](#); Amodio et al., [2004](#); Amodio et al., [2006](#)). Participants with a larger ERN to racially charged errors were more likely to slow down and become more accurate on the next trial, suggesting that they were trying to compensate to avoid such errors in the future.

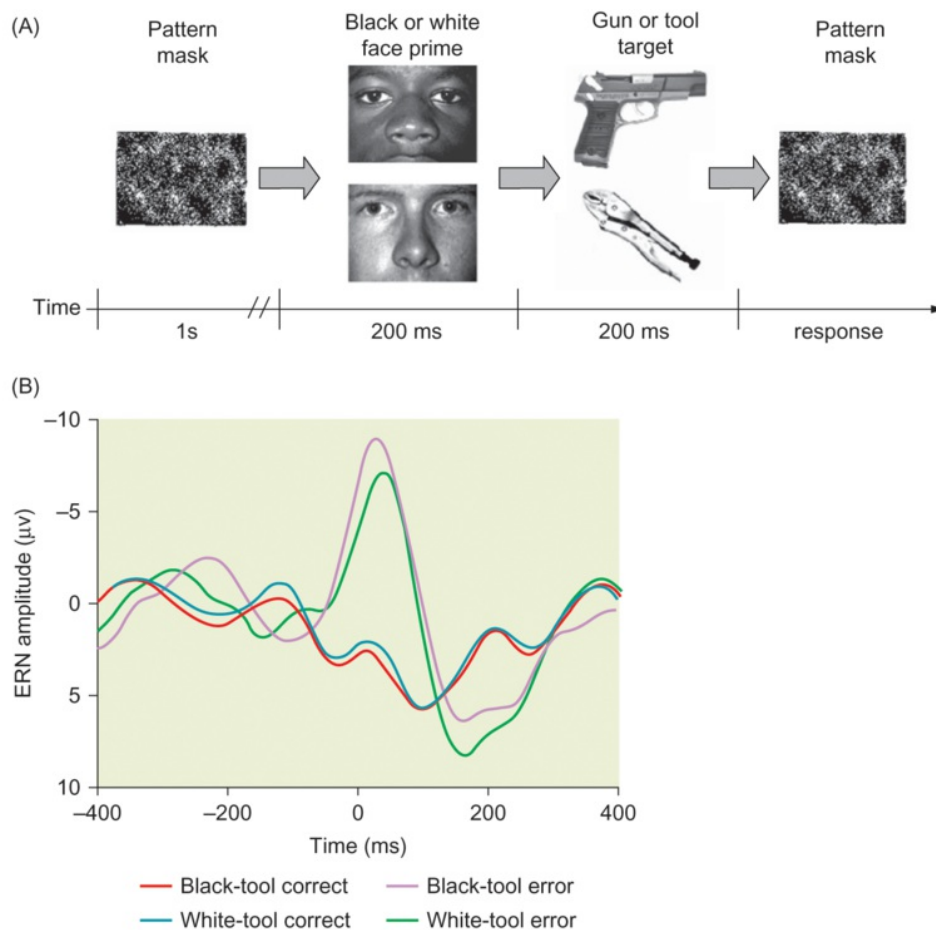


Figure 13.18 Error-related brain processes are influenced by racial meaning.

Panel (A) illustrates a task in which participants had to decide if a visual image was a gun or a tool. The image was preceded by the quick presentation of an African-American or Caucasian face (from Amodio et al., [2004](#)). Panel (B): the error-related negativity was greater when participants made black-tool errors, that is, mistakenly calling a tool a gun after being primed with a black face, compared to white-tool errors or correct responses. These data indicate that errors reflecting racial bias elicit a stronger neural response than other errors.

Other findings have tied feelings of guilt about racial prejudice to EEG asymmetries in the frontal lobe (Amodio, Devine, and Harmon-Jones, [2007](#)). In this study, participants were given false feedback indicating that they had responded in a racially prejudiced way. The feedback altered patterns of frontal lobe EEG asymmetry, toward less left-sided activity. According to the approach-withdrawal model, this is consistent with reduced approach motivation; perhaps the sense of guilt at being prejudiced made people want to pull back. However, participants who reported more guilt were also subsequently more interested in reading articles about prejudice reduction, which in turn was associated with an increase in approach-related left frontal activation. In other words, the feeling of guilt was first associated with withdrawal-related EEG asymmetries, but taking advantage of the opportunity to make amends was associated with approach-related EEG asymmetries.

These results do not really tell us why some people become more or less prone to racial prejudice. However, they do give clues about what is going on in the brain when people perceive racial cues and try to regulate their own responses to those cues. Despite the diverse neural signals and structures being studied, one general conclusion is that brain regions involved in emotion and cognitive control play an important role in these aspects of social cognition.

Stereotype Threat

An important aspect of understanding stereotyping and prejudice is appreciating the pernicious consequences that these processes can have for the members of the stereotyped group. In the most extreme cases, stereotypes can lead to danger to members of the stereotyped group. For example, participants are more likely to “shoot” an unarmed black figure in a video game than an identically unarmed white figure (Correll et al., [2002](#); Senholzi et al., [2015](#)). Other consequences of stereotypes can be more subtle, but can have long-lasting effects on people. The most well-researched example is the concept of stereotype threat.

Stereotype threat is a term coined by psychologist Claude Steele to describe how activation of a stereotype can lead to underperformance by a member of a stereotyped group (Steele and Aronson, [1995](#)). For example, if the concept of race is made especially salient, blacks perform more poorly on cognitive tasks relative to whites, compared to a control condition in which race is not made salient. Likewise, women perform more poorly on math tests if they are first reminded of their gender. According to current ideas about stereotype threat, when social categories are made salient, individuals in denigrated social categories may fear confirming society's stereotype about their category. When the stereotype involves cognitive performance – such as the stereotype that women are bad at math or that blacks are not as smart as whites – the induced stereotype threat can actually undermine cognitive performance and perpetuate the stereotype.

While the mechanisms of stereotype threat are still under investigation, researchers have proposed a number of possibilities (Schmader et al., [2008](#)). For example, the stress of being reminded of a negative stereotype may activate physiological arousal that interferes with cognitive performance. Thinking about the stereotype may also impose a cognitive load, taxing executive functioning by increasing self-monitoring and effortful self-regulation. For example, imagine a black person sitting down to take a standardized test after being subtly reminded of the stereotype that blacks do not perform as well on such tests as other racial groups. The person may become nervous about confirming the stereotype, thus increasing physiological arousal. She may also need to regulate thoughts about the stereotype (such as, “I need to try extra hard,” “I notice that not many blacks are taking this test today,” “I want to prove that I can do it,” “I wonder if I am really able to perform well,” and so on), and she may pay very close attention to her own mistakes and thought processes. Such extra cognitive baggage may interfere with performance itself.

Indeed, studies do show that stereotype reminders can change not only cognitive performance but also neural processing in members of the stereotyped group (Derks et

al., [2008](#)). For example, one fMRI study compared brain activity during a math test among women who had either been primed or not with a stereotype about women's poor math performance (Krendl et al., [2008](#)). Those in the control condition tended to show an increase in activity during the math tasks in areas known to be important in mathematical cognition, including left inferior parietal cortex and bilateral angular gyrus. In contrast, those in the stereotype threat condition instead showed increased activity in the ventral anterior cingulate, a region important in emotion regulation (see also Wraga et al., [2007](#)). ERP research has also found that neural responses to errors and negative feedback are enhanced among members of stereotyped groups performing under stereotype threat conditions, a pattern that could imply excessive self-monitoring (e.g., Forbes and Leitner, [2014](#); Forbes, Schmader, and Allen, [2008](#); see also Mangels et al., [2012](#)).

As cognitive neuroscientists, we should be particularly concerned about how scientifically (or pseudo-scientifically) framed beliefs about social groups can affect people in those social groups. One study compared women's performance on a math test when they read either an essay arguing that gender differences in math are due to genetics or an essay arguing that gender differences are due to experience (Dar-Nimrod and Heine, [2006](#)). The women performed worse on the test if they had read the essay attributing gender differences to genetics. Likewise, people were more likely to endorse gender stereotypes if they had first read that gender differences in cognition are biologically based (Brescoll and LaFrance, [2004](#)).

Thus, while understanding the neural basis of stereotype threat effects on cognition is worthwhile in and of itself, it is also important for scientists to be aware of how scientific theories about the biology of cognition can have unintended consequences for members of stereotyped groups. That is, people's beliefs about the supposed neuroscientific basis of a group difference, whether true or not, can affect their actual cognitive performance. In general, the study of stereotyping from a neuroscience perspective can potentially help us to better understand the processes by which people

form judgments about other social groups, and can also help us to understand the consequences of stereotyping on the neural processing of those being stereotyped. Issues involving the societal implications of neuroscience research will be more fully addressed in the [final chapter](#).

Summary

Social Brain Hypothesis

- Many scientists believe that the primate brain evolved to be disproportionately large, compared to other species, in order to support processes of social cognition that are necessary for successful group living.

Social Influence

- People have a tendency to shift their judgments in line with the judgments of other people, a phenomenon known as conformity. Conformity may function to increase the correctness of judgments (informational conformity) or to enhance group belongingness (normative conformity).
- Neural mechanisms of conflict detection, that is, in the anterior cingulate cortex, are activated when people perceive that their judgments differ from those of a social group. Conversely, reward pathways are activated when people perceive that their judgments align with the judgments of a social group.
- Social norms describe written or unwritten rules of social behavior, including codes of etiquette as well as formal laws governing behavior. Deviance from social norms is a characteristic of some clinical conditions, such as orbitofrontal brain damage, Tourette's syndrome, and autism. Deviance may result from a variety of processing difficulties, including difficulties in the comprehension of or memory for norms, motivation to comply, or inhibitory control needed to comply.

- Economic games, such as the ultimatum game, have been used to study social norm compliance. Such games focus on the “fairness norm,” the idea that rewards should be fairly shared. Perceived violations of the fairness norm are associated with activity in regions involved in disgust and conflict processing.
- When a person is deciding how much to share in an economic game, the orbitofrontal cortex may assist in representing the potential costs of unfair behavior. Manipulations of activity in lateral prefrontal cortex during decisions about sharing can shift behavior toward selfishness or altruism.

Understanding Other Minds

- One way that we understand the mental states of others is through mimicking those states. Mimicry, or imitation, calls upon regions in the “mirror neuron system,” including inferior frontal cortex. The degree of mimicry or mirroring can depend on the degree of interpersonal similarity or closeness between two people.
- Theory of mind describes the ability to understand the beliefs of others, even when those beliefs are known to be false. Theory of mind is assessed with a variety of tasks, including the classic false belief task, which tends to activate both the temporoparietal junction and medial prefrontal cortex.
- Empathy can be considered to have three main aspects: emotional contagion, cognitive perspective-taking, and pro-social behavior. Emotional contagion draws primarily upon neural mirroring processes, whereas cognitive perspective-taking draws primarily upon processes of mentalizing in the temporoparietal junction and medial prefrontal cortex. Pro-social behavior has not been as well studied from a cognitive neuroscience perspective.
- The ability to understand other minds may have evolved to make social environments more predictable and to enable the social bonding, cooperation and group problem solving necessary for group-living primates.

- We can mentalize about ourselves as well as mentalizing about others, and doing so activates overlapping regions of medial prefrontal cortex. Factors such as temporal perspective (past, present, or future self) and degree of closeness with the other person can modulate the degree to which patterns of activity are distinct when thinking about one's self versus others.

Autism and Social Cognition

- Autism spectrum disorder is currently defined by two main categories of symptoms: (1) impairment in social interaction and (2) restrictive or repetitive activities or interests. Symptoms are present in early development, evident across settings, and cannot be attributed to global intellectual delay.
- The “broken mirror theory” of autism posits that the mirror neuron system is dysfunctional in autism. Research indicates deficiencies in imitation, but those deficiencies tend to be restricted to imitation of emotional expressions.
- People with autism tend not to perceive social cues, such as facial expressions, in the same way as other people do. For example, they do not look at faces for as long, they are not as sensitive to gaze direction in the eyes, and they do not activate face processing areas such as the fusiform gyrus to the same degree as do control participants.
- People with autism have difficulty with mentalizing tasks, such as the false belief task. On even simple mentalizing tasks such as the Heider-Simmel illusion, people with autism do not show the normal degree of activation in mentalizing regions such as temporoparietal junction and medial prefrontal cortex.
- People with autism may have difficulty with the cognitive perspective-taking component of empathy, but they can experience emotional contagion in response to others' emotional states and can express pro-social behavior.

Perceiving and Judging Social Groups

- People have a strong tendency to categorize others into “in-groups” and “out-groups.” Some social categories are pervasive in society (e.g., age, race, gender), and others can be established in a single experimental session based on seemingly trivial differences between people.
- ERP studies indicate that social categories such as race and gender are distinguished very quickly (within about 200 ms) when viewing faces or other social stimuli.
- People tend to show stronger empathic responses, measured both behaviorally and neutrally, to others whom they perceive to belong to their own “in-group.”
- Stereotyping refers to the tendency to assume that certain characteristics are universally true of group members, whereas prejudice refers to a negative attitude about a particular social group, and discrimination refers to biased behavior toward a person depending on their social group. Biases about social groups can be implicit.
- Implicit negative biases about social groups are associated with the increased activity in the amygdala, possibly because of its role in responding to threatening information.
- Cognitive control regions, such as anterior cingulate and dorsolateral prefrontal cortex, are engaged when people try to regulate their own behavior to prevent biases.
- Stereotype threat refers to the phenomenon in which activation of a stereotype about a group leads to changes in the group members’ performance. Performing under stereotype threat conditions can alter the neural regions engaged during the task, in a pattern that suggests a decrease in activity in task-relevant regions and an increase in activity during self-monitoring regions. Thus, stereotype activation

can have consequences for cognitive performance in members of stereotyped groups.

Part III



Broader Applications

Chapter 14 [Psychopathology](#)

Chapter 15 [Brain Development and Plasticity](#)

Chapter 16 [Generalized Cognitive Disorders](#)

Chapter 17 [Cognitive Neuroscience and Society](#)

Chapter 14

Psychopathology



Schizophrenia

Symptoms and Features

Frontal Lobe

Temporal Lobe

Disruption in Functional Connectivity

What Causes Schizophrenia?

Implications for Treatment

Depression

Symptoms and Features

Frontal Lobe

Posterior Cortical Regions

Functional Connectivity Among Cortical Regions

Subcortical Regions

Therapeutic Interventions

How Standard Treatments for Depression Affect the Brain

Noninvasive Stimulation Treatments

Invasive Stimulation Treatments

In Focus: Can Your Genes Make You Unhappy?

Anxiety Disorders

Symptoms and Features

[Amygdala and Hippocampus](#)

[Cortical Regions](#)

[Regulation of Anxiety](#)

[Monitoring and the Anterior Cingulate](#)

[Verbalization and Worry](#)

[Posterior Regions and Anxious Arousal](#)

[Action Systems in Obsessive-Compulsive Disorder](#)

[Substance Abuse and Addiction](#)

[Reward Pathways](#)

[Orbitofrontal Cortex](#)

[Other Brain Regions Implicated in Addiction](#)

[Conclusions and Caveats](#)

[Summary](#)

Joe Gray joined our family when I was 15 and he was 60. He and my mother had grown up on neighboring ranches in southern New Mexico. After my father's death, he came to Philadelphia to support her. Although my brothers and I had never met him before, he became a friend, mentor, and guide. Joe lived with us until he ended his life at 72.

Although some of Joe's past is shrouded in mystery, there were certain facts of his life about which we were sure. We see him in photos as a young man astride a horse, handsome and confident. He knew how to ride and shoot and handle animals. He was a scholar and a man of intense curiosity who read widely in many disciplines. Educated at Princeton University, he studied the Spanish language. We knew that he had spent time as an undercover agent for the United States during the Cold War in South America, allowing him to combine his sense of adventure and his intellectual pursuit of Spanish, among other things, but he never told us any of the details. We also knew that he became an alcoholic and was a member of Alcoholics Anonymous for many years. When Joe came to

live with us, he had retired and had been living in Albuquerque, New Mexico. But his zest for life continued – whether going to listen to bluegrass and folk music, training a puppy, repairing a faucet, or teaching us to drive.

Joe had his first stroke when I was in graduate school. I was home for the holidays. One day we noticed that although Joe, ever talkative, was speaking, what he was saying was incoherent. Even so, he did seem to follow, more or less, what we were saying. I had enough training by then to realize that it was a symptom of a brain injury, most likely Broca's aphasia. Indeed, a neurological exam confirmed that Joe was suffering the consequences of a left-hemisphere stroke. Joe worked hard in therapy to regain his spoken-language abilities, and took comfort that reading, one of the pursuits he enjoyed most in life, was not lost. His progress was quite good – until he had a second stroke. After that, he couldn't read, or drive, or find the right words to converse. It was then that his demeanor also changed.

Although often cantankerous, Joe had always been upbeat about life, retaining his sense that life was an adventure. After the second stroke, though, his moods could be positively dark, and the energy he had once had for life noticeably ebbed. He began to threaten suicide. He tried several times. He took an overdose of pills one night but woke up eventually, in mid-afternoon, and was groggy for a day or two. He drank a fifth of scotch, after having not touched alcohol for 20 years, but passed out on the kitchen floor before any major damage was done. I convinced him to see a psychiatrist, who got him so angry that he forgot to be depressed for a while. We tried to cheer him up, telling him how important he was to our family, taking him to his favorite places, and buying him a brand-new pair of western cowboy boots.

Finally, he decided to hang himself, and this time he succeeded in his suicidal intent. My mother came home from work on a Friday afternoon to find cardboard taped to the front door window so that no one could see inside, and

Joe, having somehow fallen from the noose, lying dead on the floor in the hallway. He was wearing his new boots.

Perhaps it will come as no surprise to the reader that much of my research since graduate school has focused on the role of brain mechanisms in depression.

– Wendy Heller, clinical neuroscientist

As in other areas of cognitive neuroscience, much of what we know about the brain and mental illness has been based on observations of people with damage to the brain. The depression that led Joe Gray to suicide was most likely due to more than his inability to accept his impairments, although no doubt the loss of independence and reduced intellectual capacity contributed to his despair. Research has shown that damage to parts of the left hemisphere, especially frontal regions, often leads to clinical depression. Findings such as these underscore the importance of particular brain regions in contributing to psychiatric disorders.

Fully understanding mental illness, or psychopathology, involves much more than understanding the brain. Psychopathology can be fruitfully approached from many different psychological perspectives, including not only the biological but also cognitive, social, and cross-cultural levels. For example, a condition like clinical depression may be correlated with certain biological variables, such as deactivation of the left frontal lobe, but it can also be described as involving changes in ways of thinking and making meaning from life; it can affect and be affected by interpersonal relationships; and its appearance and manifestation can be influenced by cultural values and norms. Although the focus in this chapter is on cognitive neuroscience approaches, you should be aware that a more complete understanding of psychopathology must also include these additional perspectives.

Here our goal is to understand what unique information cognitive neuroscience can bring to understanding the complexities of mental illness. We focus on four major categories of disorders – schizophrenia, depression, anxiety disorders, and substance

use disorders – because they are among the most common and devastating of mental afflictions. Psychiatric conditions associated with development (e.g., autism, attention-deficit/hyperactivity disorder) and aging (e.g., Alzheimer’s disease) are covered in [Chapters 15](#) and [16](#), respectively.

Before we discuss these disorders in more detail, it is important to raise a significant ethical concern. You will notice throughout this chapter that, in some studies that aim to extend the understanding of mental disorders, people may be placed in situations that are somewhat provocative or difficult. For example, we will discuss studies in which depressed people are asked to listen to sad stories, people with phobias are shown things that scare them, and people with posttraumatic stress disorder are asked to think about the situation that traumatized them. The design of these studies does not mean that cognitive neuroscientists are a mean or cold-hearted bunch. Rather, their goal is to understand these disorders so that, ultimately, treatment options can be expanded and improved. Like all cognitive neuroscience studies, studies involving participants with clinical conditions must be approved by a review board. These boards ensure that the provocation is not enough to cause the individuals more distress than they would ordinarily encounter in daily life as a result of their disorder. Typically participants are also “debriefed” so that any residual distress can be detected and eliminated, and they are informed about resources available to them should any ill effects occur in the future. It is a testimony to the good-heartedness and generosity of these research participants that they are willing to be involved in such experiments. Although participating in studies may not directly help their affliction, and might even exacerbate it, they participate anyway, in the hope that it may help other people in the future with similar afflictions.

Schizophrenia

It is generally accepted that schizophrenia results from a disease of the brain, although researchers are still far from having a complete understanding of this condition.

Schizophrenia is considered a chronic condition that is managed but never really cured. It often strikes first in late adolescence or early adulthood, and requires clinical intervention and management from that point forward. Because of its chronic nature, schizophrenia accounts for half of all admissions to psychiatric hospitals, and it is one of the top 10 causes of years lost to disability worldwide (Mueser and McGurk, [2004](#); Whiteford et al., [2013](#)). Moreover, the disorder is relatively common, with approximately 1 in 200 people affected at any given time (World Health Organization, [2001](#)). These numbers give some sense of the magnitude of schizophrenia as a problem for individuals, families, and society at large. As we will see next, the variety and complexity of symptoms have made it impossible to pin down one single brain region or system as the focal point of this disorder.

Symptoms and Features

The diagnosis of schizophrenia, like that of other psychiatric conditions, is currently based on observable behavioral and psychological features, not on biological markers. In other words, there is no blood test or other biological indicator that can diagnose a person as having schizophrenia. Rather, the diagnosis is made by a trained clinician who interviews the patient and family members to ascertain the presence of certain key features that are thought to define the disorder.

According to the Diagnostic and Statistical Manual currently used by psychiatrists (DSM-5; American Psychiatric Association, [2013](#)), criteria for diagnosis of schizophrenia include at least two of the following symptoms, which have lasted for at least one month in duration: hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms, which we describe in this section. The first three items on this list – hallucinations, delusions, and disorganized speech – are deemed especially central in diagnosis, as at least one of these three symptoms must be present in order to qualify for a diagnosis of schizophrenia.

Many researchers group symptoms of schizophrenia into two main categories: positive and negative symptoms. [Positive symptoms](#) refer to excesses or distortions in

normal behavior, whereas **negative symptoms** refer to the absence of normal behavior. Positive symptoms include the presence of hallucinations, delusions, and disorganized thought and behavior that can seem strange and irrational to an outside observer. Hallucinations consist of perceiving things that are not really there, such as hearing voices in one's head or seeing "visions" or apparitions. Hallucinations in schizophrenia can occur in any sensory modality, but auditory hallucinations are most typical. Delusions are irrational beliefs, like thinking that the FBI is tapping your phones (paranoid delusion) or believing that you are the messiah (delusion of grandeur).

Negative symptoms include apathy (lack of motivation), flattened affect (lack of emotional responsiveness), and failures of volition or self-directed behavior. Much research has focused on positive symptoms, probably because they are the most florid and obviously disruptive. However, negative symptoms can also greatly interfere with the person's ability to function normally. Negative symptoms are associated with a poorer prognosis and are less easily treated by antipsychotic medications (e.g., Velligan et al., [2014](#)).

Regardless of diagnostic type, patients tend to show a combination of symptoms from a set of eight categories that are listed in [Table 14.1](#). As you can see, these symptoms cross several domains of functioning, including motor functions, perception, emotion, motivation, and executive function. Therefore, it should not be surprising that multiple brain systems are thought to be affected in this disorder.

Table 14.1 Symptom Categories in Schizophrenia

| Category | Symptom(s) |
|--------------------|--|
| Content of thought | A delusion or false belief. |
| Form of thought | A formal thought disorder involving abnormalities in the way a person's thought processes are organized. "Loose association," in which ideas shift from one unrelated topic to another, is a |

common example of this type of symptom.

| | |
|------------------------------------|--|
| Perception | Hallucinations or the reporting of experiences for which no observable eliciting stimuli appear to exist. |
| Affect | Disturbed emotions. Most common are emotions that are blunted, flat, or inappropriate to the situation. |
| Sense of self | Confusion about self-identity. The person may feel unreal or controlled by outside forces. |
| Volition | Reduced motivation and interest in pursuing almost any sort of goal. These symptoms interfere severely with a person's ability to work. |
| Relationship to the external world | Withdrawal from the external world and preoccupation with internal fantasies and odd ideas. |
| Psychomotor behavior | Abnormalities of movement, including rocking, pacing, stereotyped actions, and bizarre behavioral rituals. Some patients diagnosed with schizophrenia become almost totally immobile; others take on a disheveled look or dress oddly, against social norms. |

One of the first-noted and most reliable pieces of evidence of neural dysfunction in schizophrenia is enlargement of the lateral and third ventricles (Shenton et al., [2001](#)). Ventricular enlargement, depicted in [Figure 14.1](#), results from atrophy of brain tissue across many regions of the brain (e.g., Haijma et al., [2013](#)). As such, it is a general indicator of tissue loss rather than an indicator of abnormalities in specific brain regions. The brain may continue to atrophy for up to 20 years after the person is first diagnosed, leading some to suggest that schizophrenia may be associated with a

continuous pathophysiological process (Pol and Kahn, [2008](#)). Furthermore, longitudinal research has found that decreases in brain volume are correlated with the duration of relapses over a seven-year follow-up period, suggesting that preventing relapses may be one way to alter the deteriorating path of brain atrophy (Andreasen et al., [2013](#)).

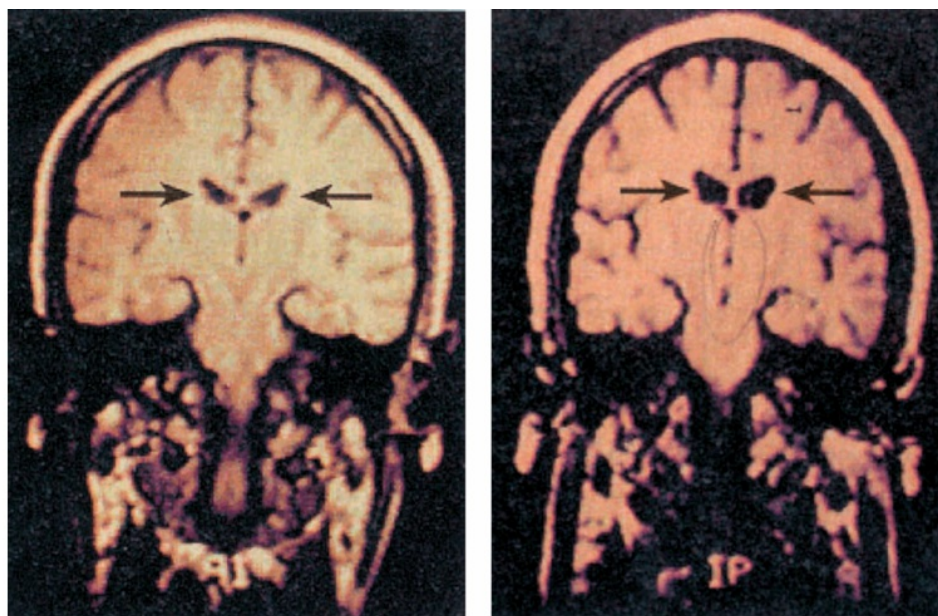


Figure 14.1 Enlargement of the ventricles in schizophrenia.

These MRIs show the brain of an individual with schizophrenia (right) and his identical twin, who is not affected by the disorder (left). Notice the discrepancy in the size of the ventricles (see arrows).

Courtesy Dr. Weinberger, NIMH, St. Elizabeth's Hospital.

To pinpoint more specific brain regions that may be implicated in schizophrenia, researchers have taken two main approaches. The first involves comparing cognitive deficits in schizophrenia to deficits in patients with known brain damage. A second approach is to use neuroimaging and other measurements of brain functioning to identify areas of difference in brain anatomy and function between schizophrenics and control groups. Both of these approaches have pointed to the frontal and temporal lobes as especially involved in schizophrenia.

Frontal Lobe

There are many indications that the functioning of the frontal lobes is compromised in schizophrenia. Many of the cognitive functions that are most disrupted in schizophrenia are dependent upon the frontal lobe, including working memory, self-monitoring, attention, cognitive control, and behavioral flexibility (Barch and Ceasar, [2012](#); Orellana and Slachevsky, [2013](#)). For example, schizophrenic patients are impaired on tests of planning and tests of mental flexibility, such as the Wisconsin Card Sorting Test (see [Chapter 11](#) for a description of this task). Not surprisingly, dozens of functional imaging studies have demonstrated hypoactivation (reduced activation) of frontal regions in individuals with schizophrenia compared to controls (see [Figure 14.2](#)). **Hypofrontality** (frontal hypoactivation) is evident in schizophrenia both when the person is quietly resting and when he or she is engaged in tasks that normally activate the frontal lobe.

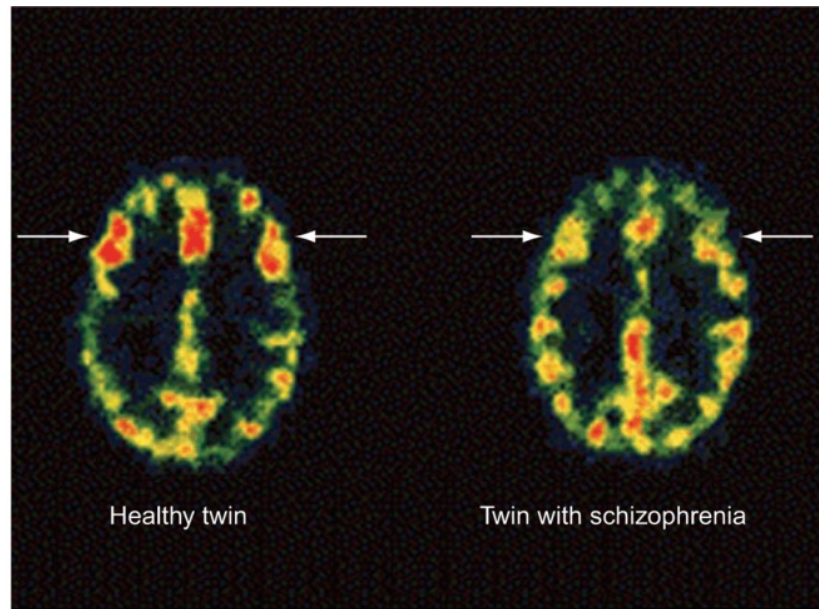


Figure 14.2 Hypofrontality in schizophrenia.

Areas of the frontal lobe (white arrows) show reduced activity in patients with schizophrenia compared with control participants, such as an identical twin who does not have the disorder. Areas with the most activity are shown in red, followed by regions shown in orange, and yellow.

Source: Daniel Weinberger, M. D., E. Fuller Torrey, M. D. (formerly of NIMH), Karen Berman, M. D. NIMH Clinical Brain Disorders Branch. Division of Intramural Research Progress, NIMH 1990.

A variety of different neurophysiological methods provide strong evidence that frontal lobe mechanisms involved in inhibiting behavior are disrupted in people with schizophrenia. One example comes from a smooth-pursuit eye-movement task in which a person must track a continuously moving target across a screen (Braff, [2004](#)). Because these eye movements are voluntary rather than involving the automatic orientation of attention, they require involvement of the frontal eye fields as well as other frontal regions (Tanabe et al., [2002](#)). Successful performance of this task requires activating the frontal systems responsible for smooth eye movements, while simultaneously inhibiting the saccadic system that would move the eye ahead of the target. People with schizophrenia tend to show a bumpy eye-movement trajectory, jumping ahead of the

target, as depicted in [Figure 14.3](#). In addition, they fail to activate the frontal eye fields as much as controls during such smooth-pursuit eye-movement tasks (Tregellas et al., [2004](#)). Schizophrenic patients also have difficulties with anti-saccade tasks, in which a stimulus appears in one location but the participant must inhibit looking at the stimulus and instead shift her gaze to the location on the opposite side of the screen (Barch, [2005](#); Braff, [2004](#)). Deficiencies on this task also indicate a problem in inhibition.

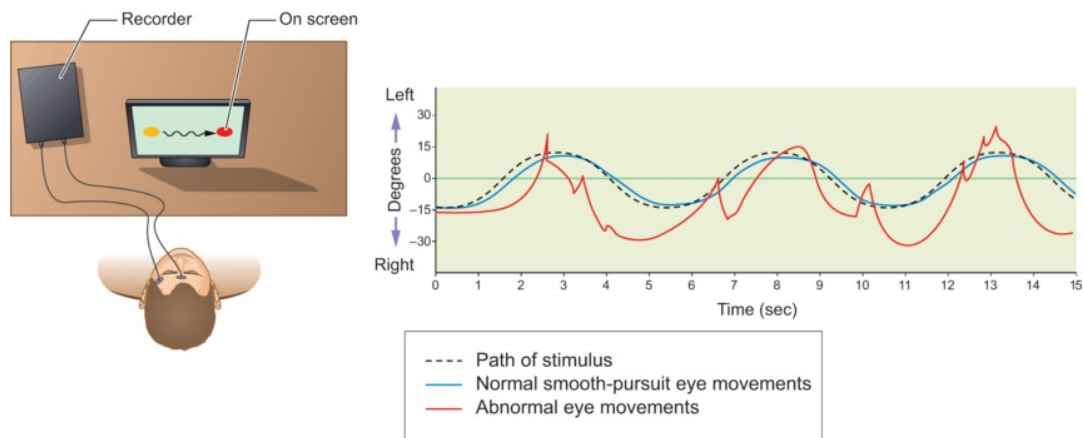


Figure 14.3 Deficient smooth-pursuit eye movements in schizophrenia.

In a task that requires the subject to visually track the path of a moving target across a screen, people with schizophrenia show an abnormal eye-movement trajectory, jumping from position to position.

As we learned in [Chapters 9](#) and [11](#), working memory depends heavily on lateral regions of the frontal lobe and may contribute to performance on many other tasks of executive function. Working memory is disrupted in patients with schizophrenia. Numerous studies have found that people with schizophrenia show abnormal activity in the dorsolateral prefrontal cortex (DLPFC) during the performance of working memory tasks, especially tasks that require the manipulation of information being held in working memory. For example, reduced activity in the DLPFC is evident when schizophrenic patients complete the N-back task of working memory, which requires holding in mind information from several previous trials in order to compare that information to the information in the current trial (Barch et al., [2002](#); Perlstein et al., [2003](#)). The ventrolateral prefrontal cortex is also underactive during the encoding phase

of working memory tasks in people with schizophrenia (Bittner et al., [2015](#)). As discussed in [Chapter 11](#), disruptions in working memory ability can compromise executive function because of reduced ability to keep a goal in mind, prioritize information to be held in memory, and sequence behavior toward a goal.

Schizophrenia is also associated with dysfunction of medial regions of the frontal lobe, especially those associated with monitoring and evaluating one's behavior. As noted in [Chapter 11](#), one method of studying self-monitoring is through the error-related negativity (ERN), the brain potential that is normally evoked immediately following an error in performance. People with schizophrenia do not show normal ERN responses to errors, indicating a failure to effectively evaluate their own performance (Mathalon et al., [2002](#)). These findings fit well with other studies demonstrating abnormalities in the structure and function of the anterior cingulate cortex in schizophrenia (e.g., Kerns et al., [2005](#); Wang et al., [2007](#)).

A fascinating study using noninvasive brain stimulation suggests that altering activity in medial prefrontal cortex can improve self-monitoring and performance in people with schizophrenia (Reinhart et al., [2015](#)). Researchers found that stimulating the medial prefrontal cortex with tDCS in people with schizophrenia both increased their ERN responses to errors so that they better matched ERN responses of a control group, and also improved their behavioral performance on a trial-and-error learning task. This evidence implies that deficiencies in self-monitoring by medial prefrontal cortex may contribute to poor cognitive performance in people with schizophrenia.

Temporal Lobe

Although many studies have focused on the frontal lobes, other evidence indicates that posterior regions of the brain are also abnormal in schizophrenia. Intuitively, this should make sense if you think about the symptoms of schizophrenia. For example, hallucinations are usually auditory in nature, and auditory processing is performed by the temporal lobes. In addition, the loose and disorganized language production by schizophrenics is often described as similar to the “word salad” style characteristic of

people with Wernicke's aphasia, who typically have damage to posterior regions of the temporal lobe (see [Chapter 8](#)).

Some of the evidence for dysfunction of temporal and posterior brain regions comes from anatomy. For example, even in people who have just experienced their first episode of schizophrenic behavior, there is a reduced volume of gray matter in the left and right middle temporal gyrus, left posterior superior temporal gyrus, and left angular gyrus (see [Figure 14.4](#); Haijma et al., [2013](#); Honea et al., [2005](#)). Some of this gray-matter loss worsens during the course of the disease.

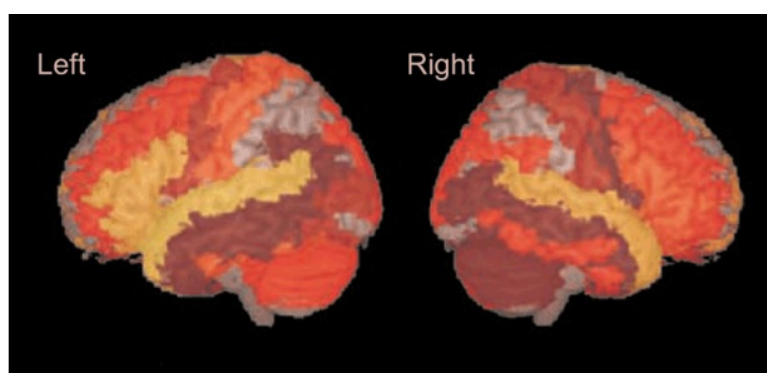


Figure 14.4 Reduced gray-matter volume in schizophrenia.

This figure shows areas of gray matter that were found, in numerous studies, to be reduced in individuals with schizophrenia compared to those without the disorder. Areas shown in yellow show the most consistent findings across studies, followed by areas shown in orange and dark red. Notice how the regions that most reliably exhibit volume reductions across many studies are the superior temporal gyrus in both hemispheres and the inferior frontal areas of the left hemisphere. Also notice that much of the frontal lobe is depicted in orange, indicating that studies also point to reduced gray matter in these areas, but not as reliably across different studies.

From “Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel based morphometry studies,” by R. Honea, T. J. Crow, D. Passingham, and C. E. Mackay, *American Journal of Psychiatry*, 162, [2005](#). Reprinted with permission from the American Journal of Psychiatry, Copyright (2005) American Psychiatric Association.

These anatomical differences have been linked to functional deficits measured using ERP and MEG methods. For example, people with schizophrenia filter incoming information in the auditory modality in a different manner than controls. Normally, when two successive auditory tones or clicks are presented, the neural response to the second one is less than the response to the first, a response known as [sensory gating](#). It makes sense that our brain gates information in this way, because it allows the brain to attend to new information rather than becoming stuck on information it has already registered. Imagine what life would be like if you couldn't do such gating. For example, when you noticed a clock ticking in the background, each tick would capture your attention in the same way as the first, and you'd never become accustomed to the ticking.

Sensory gating can be measured through an early event-related potential, the P50, which occurs within 50 ms following an auditory stimulus like a click. The reduced P50 response to the second stimulus in a paired sequence is thought to represent an inhibitory process that allows very early attentional selection within the auditory system (see [Figure 14.5](#)). Many studies have demonstrated that this inhibition effect is absent in schizophrenics, indicating a disturbance in sensory gating (e.g., Hazlett et al., [2015](#); Owens et al., [2016](#); Patterson et al., [2008](#)).

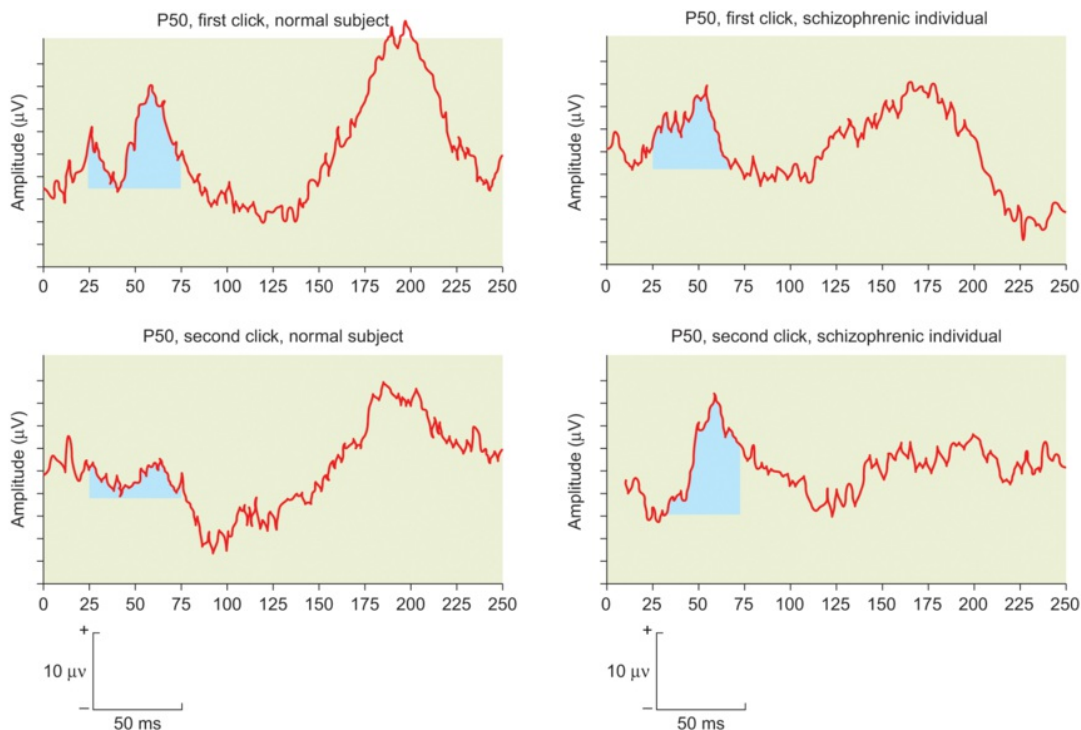


Figure 14.5 Deficits in sensory gating in schizophrenia.

In normal people (left panels), the neural response evoked by the second click (bottom row) in a pair of auditory clicks is reduced, compared to the response to the first click (top row). This reduction in response is not observed in people with schizophrenia (right panel), indicating deficient gating of sensory information.

(from Braff, [2004](#))

Another electrophysiological abnormality that has been clearly demonstrated in schizophrenia is a reduced P300 response to stimuli, particularly in the auditory domain (Ford, [1999](#); Turetsky et al., [2015](#)). [Figure 14.6](#) depicts this phenomenon. As discussed in [Chapter 3](#), the P300 is an event-related potential that is elicited when a person must pay attention in order to detect a specific task-relevant stimulus within a stream of stimuli. It is thought to represent a process related to the updating of information in working memory. Schizophrenic patients tend to have a reduced P300 over many brain regions, but particularly over the left temporal lobe. This functional deficit may result from less gray matter in the region that generates the P300 response, as patients with a relatively smaller left planum temporale tend to also exhibit a relatively smaller left-

sided P300 response to auditory stimuli (McCarley et al., [2002](#)). Notably, a smaller P300 response over the left superior temporal gyrus predicts more severe positive and negative symptoms (Kawasaki et al., [2007](#)). These results imply that the reduced P300 and the reduced left-sided volumetric findings may reflect a common pathology that contributes to the clinical presentation of the disorder.

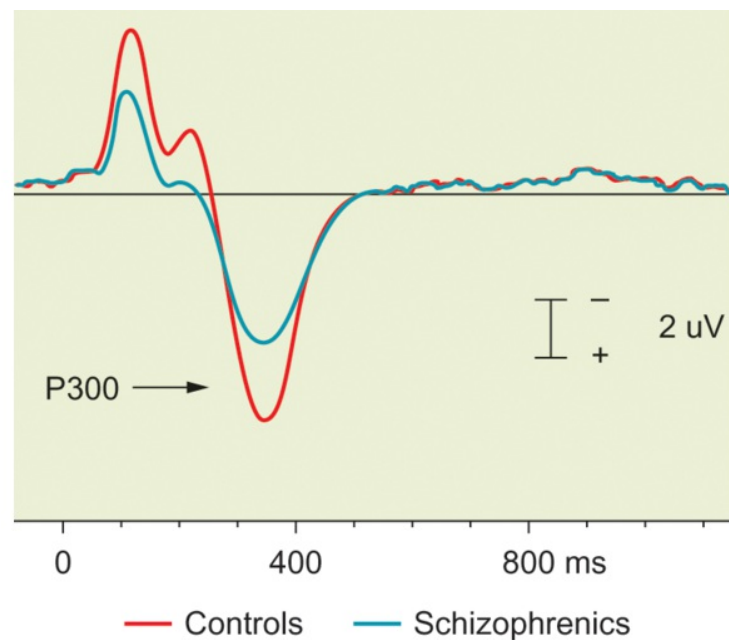


Figure 14.6 Reduced P300 component in schizophrenia.

Stimuli that normally produce a large P300 peak in the ERP waveform do not do so in people with schizophrenia.

(from Ford, [1999](#))

Electrophysiological measures of altered semantic processing in schizophrenia also provide evidence of temporal lobe dysfunction. Disorganized thinking is a clinical symptom of the disorder, and it can take the form of very loose associations between concepts, leading to incoherent speech. Consistent with this clinical symptom, cognitive studies have found abnormalities in semantic priming in schizophrenia. In semantic priming tasks, participants have to decide quickly whether a particular item is a word or a nonword, and they are faster to do so when the target item is preceded by a semantically related prime. For example, participants are faster to decide that “NAIL”

is a word if they have just been primed with “HAMMER” rather than an unrelated word such as “APRICOT.” When there is a delay between the prime and the target, people with schizophrenia tend to show reduced priming (Minzenberg et al., [2002](#)). However, other studies have revealed “hyperpriming” in people with schizophrenia when primes are followed quickly by targets (e.g., Safadi et al., [2013](#)). Together, the abnormally enhanced priming at short delays and reduced priming at long delays imply alterations in the spread of activation between associated mental concepts, making some associations stronger than normal and others weaker than normal.

ERP studies of the N400 peak during semantic priming tasks provide further evidence of schizophrenia-related abnormalities in priming. In control participants, the amplitude of the N400 peak tracks semantic relatedness, with the peak largest for unrelated prime–target pairs and smallest for related prime–target pairs. However, people with schizophrenia do not show this pattern (Kiang et al., [2008](#)). In other words, the brains of the patients do not differentiate as well between concepts that are highly related and those that are unrelated. Moreover, neuroimaging studies indicate that people with schizophrenia show abnormally increased activity in both the temporal cortex and inferior frontal cortex during priming tasks (Kuperberg et al., [2007](#)), implicating these regions as a possible neural substrate of the loose and disjointed thinking that is often characteristic of schizophrenia.

Disruption in Functional Connectivity

As we have learned, functioning is disrupted in both the frontal and temporal regions in schizophrenia. But even beyond that, recent research suggests that a disruption in communication or synchronization of activity between brain regions may also contribute to the disorder. Disrupted functional connectivity may play an especially important role in contributing to disorganized thought.

Anatomical research has contributed to the evidence for abnormal functional connectivity in schizophrenia. As you remember, myelination of white-matter tracts

allows communication between distant brain regions. Such white-matter tracts show reduced integrity, as measured by diffusion tensor imaging, in people with schizophrenia compared to neurologically normal people (e.g., Bohlken et al., [2016](#); Brambilla et al., [2005](#); Buchsbaum et al., [2006](#)). These effects may arise from abnormal expression of genes that contribute to myelination (Chavarria-Siles et al., [2016](#)).

Functional connectivity (correlations in activity between brain areas) is also altered in people with schizophrenia. Even in a resting state, functional connectivity is abnormal in schizophrenia, with studies reporting altered connectivity within the default mode network, between different subregions of the frontal cortex, and between cortical and thalamic areas (Sheffield and Barch, [2016](#)). Altered functional connectivity during cognitive tasks has also been reported. For example, during performance of working memory tasks, people with schizophrenia exhibit altered correlations between activity in the hippocampus and the dorsolateral frontal cortex (Bühner and Meyer-Lindenberg, [2017](#)).

Some studies have examined the synchrony of EEG oscillations across different brain regions, and have found reduced synchrony, particularly in the high-frequency gamma band (40–55 Hz) of the EEG (Lee et al., [2003](#)). Activity in the gamma band is thought to reflect processes that enable features of an object to be bound together to form a perceptual whole. In a visual perception task that required binding of perceptual features, schizophrenic patients tended to show less EEG gamma synchrony than controls (Spencer et al., [2003](#); see also Wilson et al., [2008](#)). In addition, researchers have found that applying a TMS pulse to the motor cortex results in abnormal “ripples” of oscillatory EEG activity that spread to a greater extent across remote brain regions in schizophrenic compared to nonschizophrenic participants (Frantseva et al., [2014](#)).

One fascinating hypothesis suggests that disruptions in the connectivity between frontal and temporal regions may contribute to the experience of hallucinations. Imagine what might happen if frontal regions that generate speech communicate poorly with the temporal lobe regions that perceive speech. A person with this disconnection may lack a

mechanism to differentiate internal speech – the kind of “talking to myself” thoughts that we all have constantly – from actual speech. Instead, the person may perceive the voice as coming from someplace else, as is typical of schizophrenic hallucinations.

Some evidence for this view comes from a study that examined EEG synchrony while people either talked aloud or listened to speech (Ford et al., [2002](#)). In control participants, synchrony between frontal and temporal sites was increased during talking compared to listening, presumably because talking engages both speech generation mechanisms in the frontal lobes and speech perception mechanisms in the temporal lobes. However, people with schizophrenia – especially those prone to auditory hallucinations – did not show this increase in frontal-temporal synchrony during talking.

A functional MRI study also found that during a task that required a word to be internally generated, activity in left frontal and temporal regions was less tightly correlated among participants with a greater severity of hallucinations (Lawrie et al., [2002](#); see also C┐┐urc'ic'-Blake et al., [2013](#)). This functional disconnection may result from altered anatomical connections. In particular, the arcuate fasciculus, a white-matter tract that connects frontal and posterior language regions, is atypical in patients who tend to hallucinate (Hubl et al., [2004](#)). These studies imply that anatomical changes may lead to functional disconnections that underlie certain symptoms of schizophrenia, such as hallucinations. Alternatively, certain kinds of symptoms may lead to decreased utilization of certain anatomical pathways, which in turn affects the development of those pathways.

What Causes Schizophrenia?

One of the most pressing questions about any mental illness is its etiology, that is, its cause (or causes). So far we have described numerous neurocognitive dysfunctions in schizophrenia – but what causes those dysfunctions in the first place? What factors operating during development lead to the profile of cognitive and neural function that we have just described?

As with many disease conditions, genes play an important role in the development of schizophrenia. Data indicate that the risk of developing schizophrenia is increased if a first-degree relative (particularly an identical twin) has the disorder (Gottesman, 1991; McDonald and Murphy, 2003). [Figure 14.7](#) illustrates the increasing risk of the disease with increasing biological relatedness to someone who suffers from it.

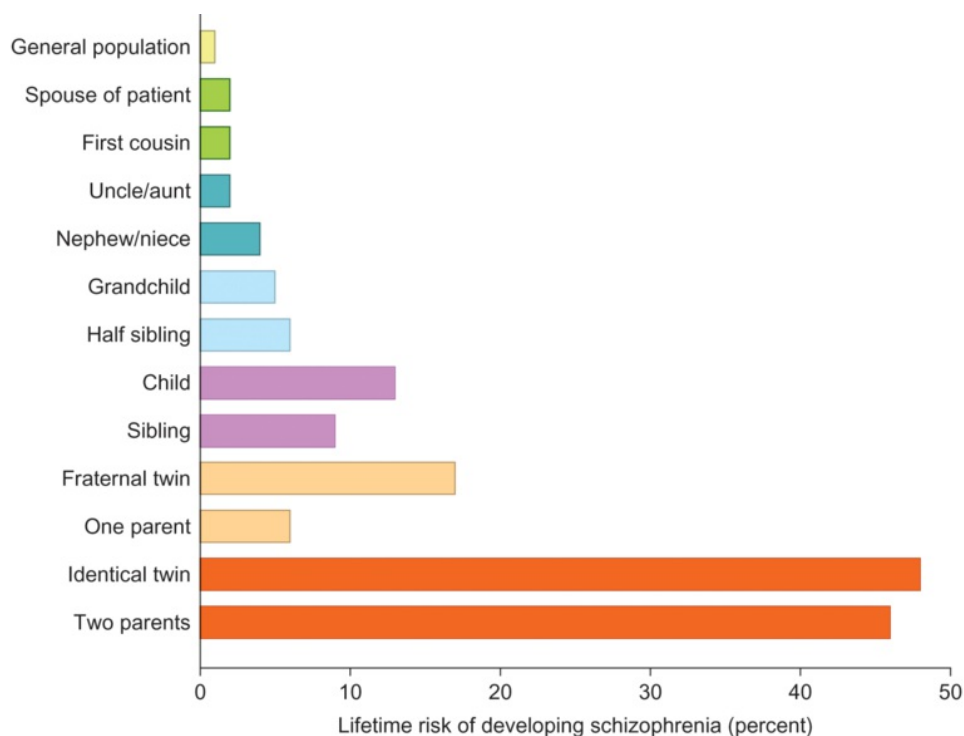


Figure 14.7 Risk of developing schizophrenia depends on relatedness to someone with the disorder.

Notice, for example, that the risk of developing schizophrenia is much higher if one has an identical twin with schizophrenia, compared to if one has a sibling with the disorder. Identical twins share all their genes, whereas siblings share only half of their genes, on average.

According to current models, genetic risk combined with exposure to certain environmental risk factors can lead to the development of schizophrenia (Davis et al., 2016). Environmental risk factors may include low exposure to vitamin D prenatally, childhood trauma, viral infections, and nicotine use. In addition, recent evidence indicates that using certain forms of cannabis can trigger psychosis among people with a

genetic vulnerability to schizophrenia (e.g., Sherif et al., [2016](#)). Various environmental factors likely interact with one another, as well as with genetic vulnerabilities, in complex ways to increase likelihood of developing the condition.

Interestingly, many of the neurocognitive characteristics of schizophrenia can also be observed to some degree in the first-degree relatives of those afflicted with schizophrenia, even when those relatives do not have a diagnosis of schizophrenia themselves. Compared to control groups, people with a close relative who suffers from schizophrenia show reduced prefrontal gray-matter volume (Brent et al., [2013](#)), altered sensory gating (Earls et al., [2016](#)), and altered frontal activity during cognitive tasks (e.g., Fusar-Poli et al., [2011](#); Seidman et al., [2006](#)). However, such effects are generally not as large as the effects observed in people with schizophrenia. These findings suggest that shared risk factors contribute to a continuum of schizophrenia-like traits among relatives, rather than determining schizophrenia as an “all or none” phenomenon.

Studies of monozygotic (identical) twins may help researchers to determine which neural differences associated with schizophrenia are due to genetic vulnerability versus which are uniquely associated with the manifestation of the disease. Specifically, researchers can study identical twins who are either concordant for schizophrenia (both twins have the condition) or discordant for schizophrenia (only one twin has it). For example, one study found that some frontal lobe abnormalities were evident in both twins regardless of their schizophrenia status, implying a shared genetic vulnerability, whereas other frontal lobe abnormalities were evident only in the twin who developed manifest symptoms of schizophrenia (Ettinger et al., [2010](#)).

Most researchers agree that a disorder as complex as schizophrenia cannot be explained by a single gene, or even a small number of genes. Genetic linkage studies have identified dozens of chromosomal regions that seem to differ between individuals with schizophrenia and those without, though results have varied across studies (e.g., Kavanagh et al., [2015](#); Purcell et al., [2009](#); Ripke et al., [2014](#); Schizophrenia Psychiatric Genome-Wide Association Study Consortium, [2011](#); Sekar et al., [2016](#)). Some of the genes linked to schizophrenia are related to synaptic pruning during

development, others are related to immune function, still others are related to dopaminergic transmission or glutamate function, and others have unknown functions.

As we discuss later, dopaminergic drugs are often used to treat schizophrenia, so schizophrenia-linked genes that affect the dopamine system, such as those that code for the D₂ dopamine receptor and the enzyme catechol-O-methyltransferase (COMT) have been of special interest. Some studies suggest that individual differences in the COMT gene, which influences dopamine metabolism, may contribute to cognitive function in both normal and schizophrenic patients. For example, in combined samples of normal and schizophrenic people, a particular COMT gene variant, the val genotype, predicts poorer performance on tasks of frontal lobe function (Egan et al., [2001](#)), as well as more deficient sensory filtering (Lu et al., [2007](#)). However, because individual differences in the COMT gene have not been consistently linked to the presence of schizophrenia (Ripke et al., [2014](#)), it is unclear whether the COMT gene plays a role in causing the disorder, or whether its role is better understood as making certain cognitive symptoms worse among those who already have the condition. These nuances illustrate the complexity of attempting to relate individual gene variants to complex clinical conditions.

One framework for thinking about the etiology of schizophrenia is the [neurodevelopmental hypothesis](#). This hypothesis argues that neural connectivity and biochemical function are altered in subtle ways from an early age, leaving the individual with a vulnerable neural organization (Brent et al., [2013](#); Rapoport et al., [2005](#)). According to this hypothesis, the disorder will become “unmasked” later in life, after puberty or at the onset of young adulthood. The unmasking is thought to occur because of some combination of adverse or stressful environmental conditions, the increased demand placed on the brain by the broader repertoire of behaviors required in adulthood, and maturational changes in the brain during adolescence and young adulthood.

Supporting the neurodevelopmental hypothesis, studies have found that people with schizophrenia have minor physical anomalies (associated with atypical prenatal

development), cognitive and neurologic deficits that precede the first psychotic episode, a family history of difficult births, exposure to viruses in utero, and anatomical brain abnormalities in both the formation of brain structure and cellular organization (Brent et al., [2013](#); Rapoport et al., [2005](#)). All of these findings implicate an abnormal developmental process that precedes the first onset of schizophrenic symptoms.

One particularly imaginative study demonstrated the early developmental signs of schizophrenia by obtaining childhood home movies from adults with schizophrenia and their nonschizophrenic siblings. The researchers had doctors rate the number of abnormalities in neuromotor behavior of the children seen in the home movies; crucially, the doctors did not know whether the child was later diagnosed with schizophrenia. The neuromotor behavior of children who later developed schizophrenia was rated as more abnormal than that of their nonschizophrenic siblings, even though the movies were taken long before the identifiable onset of schizophrenic symptoms (Walker et al., [1994](#)). However, early neuromotor abnormalities cannot predict with certainty who will develop schizophrenia, because such abnormalities are sometimes seen in children who do not develop schizophrenia. In other words, these early behaviors are not diagnostic of schizophrenia. As an analogy, pneumonia is usually accompanied by a cough, but having a cough does not mean that a person has pneumonia. Likewise, people with schizophrenia usually have neurodevelopmental abnormalities, but such abnormalities are not specific to schizophrenia.

Other evidence suggests that neurodevelopmental changes in puberty may also be related to schizophrenia (Walker and Bollini, [2002](#)). Hormones affect how genes are expressed, which in turn can affect neuronal function and development. Some theories suggest that potential changes in synaptic connectivity or pruning relatively soon after puberty may occur atypically in individuals with schizophrenia. Because adolescence is presumed to be a time of changes in dopamine activity (Sisk and Foster, [2004](#)), others have suggested that dysregulation of the dopamine system is associated with the onset of schizophrenic symptoms. Some researchers have argued that individuals who later develop schizophrenia are characterized by reduced prefrontal control over striatal

dopaminergic transmission, which in turn causes schizophrenic behavior, such as hallucinations and delusions (Heinz et al., [2003](#)).

Although the exact anatomical and neural changes that lead to the first onset of schizophrenic symptoms are not yet clear, it is clear that schizophrenia is associated with brain changes during development. For example, as shown in [Figure 14.8](#), children and adolescents who show schizophrenic symptoms at an early age have already suffered gray-matter loss. This gray-matter loss occurs throughout the cortex, with the greatest loss beginning with posterior regions and then moving forward to encompass the frontal lobes (Thompson et al., [2001](#)). The gray-matter loss continues progressively throughout adulthood, leading to accelerated brain aging in people with schizophrenia (Schnack et al., [2016](#); Vita et al., [2012](#)).



Figure 14.8 Gray-matter volume loss in schizophrenic and nonschizophrenic children and adolescents.

A longitudinal study followed participants from 13 to 18 years of age, collecting MRI scans at two-year intervals. Results showed that the loss of gray matter (measured here as % loss per year) across widespread cortical regions was pronounced in adolescents with schizophrenia compared to typical adolescents.

(from Thompson et al., [2001](#))

Implications for Treatment

One of the biggest challenges for researchers is to translate basic scientific findings into more effective treatments for mental disorders. Because various pieces of evidence point to disruption of the dopaminergic system, the most common form of treatment for schizophrenia is the administration of antipsychotic drugs that affect the dopamine systems of the brain, particularly the D₂ dopamine receptor (see [Chapter 1](#)) (Lally and MacCabe, [2015](#); Tamminga and Ivleva, [2013](#)). These drugs are effective in reducing the positive symptoms of schizophrenia, but they are relatively ineffective at reducing the negative symptoms. In addition, drugs commonly used to treat schizophrenia can have unwanted side effects, such as tardive dyskinesia (involuntary jerky movements) or metabolic symptoms (such as weight gain and changes in the body's glucose regulation). Therefore, researchers are currently investigating other pharmacological interventions, such as those that affect glutamate functioning or cannabinoid receptors (Lally and MacCabe, [2015](#)).

Given the limitations of current pharmaceutical interventions, what role can cognitive neuroscience play in guiding the search for new treatments? One implication of cognitive neuroscience research is that cognitive deficits should be targeted for treatment in schizophrenia (Braff and Light, [2004](#); Gold, [2004](#); Moore et al., [2013](#)). This is particularly crucial because severe cognitive deficits measured in the laboratory are correlated with poor real-life functional outcomes and poor quality of life in schizophrenia (Green et al., [2004](#); Ritsner, [2007](#)).

In recent years, researchers have examined the possibility that cognitive training can be an effective intervention for schizophrenia (see McGurk et al., [2007](#), for a review and meta-analysis). For example, one cognitive training study focused specifically on training in speech perception and other aspects of auditory processing (Fisher et al., [2009](#)). Patients with schizophrenia were randomly assigned to the auditory training or to a control group that played computer games for an equivalent amount of time. After 10 weeks of training, participants in the training group showed improved performance on

measures of verbal learning, memory, and cognitive control (see also Fisher et al., [2010](#)).

Further research will be needed to discover whether such cognitive interventions only affect cognitive performance, or whether they can also lead to a decrease in clinical symptoms. Additional research will also be necessary to determine how such training affects the structure and function of brain regions. For example, auditory skills depend on temporal lobe regions that are known to be deficient in schizophrenia, so future research will likely focus on how this region of cortex is influenced in a beneficial way by auditory training.

Another implication of cognitive neuroscience research is that when researchers are evaluating whether a new biological treatment (such as a new drug) is effective in treating schizophrenia, they should assess whether it improves cognitive functioning. One test of whether a drug “works” in treating schizophrenia is whether it affects not only classic positive and negative symptoms, but also specific cognitive functions compromised in schizophrenia, such as attentional filtering or working memory. For example, an effective drug should improve performance on anti-saccade and working memory tasks, lead to a larger P300 response to stimuli, and normalize the P50 inhibition effect. These cognitive and neural markers provide quantifiable measures for researchers to use when evaluating whether a drug is successful in offsetting some of the deficits observed in schizophrenia.

As a good example of the development of possible new treatments, research has found that nicotine may have beneficial effects on some cognitive symptoms of schizophrenia. As you may know, nicotine has the ability to heighten attention (a benefit that, of course, does not outweigh the negative effects of smoking). Astute clinicians observed that more than 90% of individuals with schizophrenia smoke tobacco, a potent source of nicotine. This led them to consider whether people with schizophrenia might have abnormal functioning of a nicotinic receptor. Smoking, they reasoned, might be self-medicating. Further research indicated that the alpha-7 nicotinic receptor and variations in its gene expression are linked to the effectiveness of inhibitory function of

neurons in the hippocampus. More recently, researchers have found that treatment with an agonist of this nicotonic receptor improves behavioral performance, such as reducing eye-movement abnormalities, while also reducing hippocampal hyperactivity and normalizing activity in the default mode network in people with schizophrenia (Wylie et al., [2016](#)).

Cognitive neuroscience findings also point to relevant systems to study in animal models of schizophrenia (Moore et al., [2013](#)). Novel pharmaceutical treatments are usually first tested on other animals before they are tested on humans. One obvious problem with animal models of schizophrenia is that it is hard to know what a hallucination or delusion might look like in a mouse. However, some of the cognitive deficits that we have discussed, such as working memory or attentional deficits, can be modeled in other species. Likewise, neural regions that are implicated in schizophrenia, such as the frontal and temporal regions, exist in other species (although not always in the same form as humans). Therefore, when trying to ascertain whether a new drug might work to treat schizophrenia in humans, researchers can first see whether animal studies show that the drug affects cognitive and neural systems similar to those implicated in schizophrenia in humans.

Finally, cognitive neuroscience findings may suggest interventions that target specific brain regions. Because schizophrenia is known to affect several specific regions of the brain (i.e., frontal and temporal lobes), the ideal treatment should target those regions specifically. One avenue for treatment that is currently being explored is TMS, which involves magnetic stimulation of localized brain regions (see [Chapter 3](#)). Initial studies of TMS applied over frontal and temporoparietal regions have shown mixed effectiveness in treating schizophrenic symptoms (Dougall et al., [2015](#)). Further research will be necessary to determine whether interventions that affect localized brain regions hold promise for treating schizophrenia.

Depression

Depression is one of the most common mental illnesses. It afflicts approximately 1 in 10 adults within any given 12-month period, with a rate that is approximately twice as high for women as for men (Kessler et al., [2005](#); see also Ferrari et al., [2013](#)). Some public health studies suggest that the cost of depression rivals that of heart disease, and depression often worsens other health conditions (Andrews and Titov, [2007](#); Moussavi et al., [2007](#)). The first episode of depression that a person experiences is often tied to a severe life stress, such as bereavement or job loss, but subsequent depressive episodes may appear to be decoupled from discrete life stressors (Hammen, [2005](#)). In many cases, then, depression can be considered a chronic disease. In this section we consider the major characteristics of depression, and how cognitive neuroscience can shed light on this disorder.

Symptoms and Features

One issue that complicates research on depression is the vast array of symptoms, subtypes, and variations. Generally speaking, depression is a mood disorder characterized by chronic feelings of sadness and hopelessness and loss of interest or pleasure in activities that once were enjoyed. Other typical symptoms include poor appetite or overeating, insomnia (difficulty falling asleep or early-morning awakening) or hypersomnia (too much sleeping), low energy, slowed thinking and actions, low self-esteem, poor concentration and difficulty making decisions, and suicidal thoughts (DSM-5, American Psychiatric Association, [2013](#)). As you can see, these symptoms encompass many domains of functioning, including affect, motivation, cognition, and regulation of the body's homeostatic systems.

While these features describe major depression, variations are also possible. A milder state of chronic depression lasting at least two years has been termed [dysthymia](#). Depression can be seasonal, with a typical onset during mid-fall as the days quickly grow shorter and relief in the spring as the days quickly grow longer. Depression can also be interspersed between periods of mania. During manic episodes, the person often experiences euphoria, rushes of energy, reckless impulses to engage excessively in

pleasurable activities such as sex and shopping, irritability, racing thoughts, and a sense of grandiose power. When mania occurs, either alternating with a depressive episode or occurring alone, a person is described as having bipolar disorder. At this point, it is unclear whether all of these variations of depression share similar neurocognitive characteristics, or whether each should be considered a unique entity. For present purposes, our discussion will focus primarily on major depressive disorder, the defining features of which include a profound negative mood, lack of interest in pleasurable activities, and feelings of helplessness and hopelessness.

Cognitive characteristics of depression have been well studied, and offer some clues to possible neural systems that may be disrupted. Most notably, memory and attention are biased toward negative events and interpretations in ways that create a self-perpetuating cycle of rumination about negative experiences (Disner et al., [2011](#); Mineka et al., [2003](#)). Further, people with depression often perform poorly on standard tasks of executive functions (Snyder, [2013](#)). Depressed people tend to recover poorly from mistakes and have difficulty with negative feedback, for example, showing increasingly poor performance after making errors (Murphy et al., [2003](#); Steele et al., [2007](#)). Finally, depressed individuals exhibit relatively poor performance on tasks that depend on the right hemisphere, such as judgment of line orientation, three-dimensional constructional skills, face recognition, and spatial association learning (Levin et al., [2007](#)). As you can see, multiple domains of cognition are affected by depression, implicating multiple brain regions (Clark et al., [2009](#)).

Frontal Lobe

Many subregions of the frontal lobe have been identified as functioning atypically in depression (see Singh and Gotlib, [2014](#), for a review). These regions include brain systems involved in cognitive control, such as the dorsolateral prefrontal cortex and dorsal regions of the anterior cingulate cortex, as well as regions involved in emotional aspects of processing, such as the subgenual region of the cingulate cortex (i.e., region below the genu or curve in the anterior part of the corpus callosum).

Some cognitive features of depression that we reviewed in the [previous section](#) point to impaired functioning of the executive control systems of the frontal lobe. For example, depressed people have trouble shifting mental sets – they often get stuck in maladaptive ways of thinking. Likewise, such patients can have difficulty in changing strategies when they make errors or receive negative feedback. As we learned in [Chapter 11](#), the dorsolateral prefrontal and dorsal anterior cingulate cortex are especially important for these functions. Not surprisingly, brain imaging studies have found reduced activity in these regions in people who are depressed (Singh and Gotlib, 2014).

Dysfunctions in the cognitive control systems of the frontal lobe may contribute to poor performance in people with depression. In one study, depressed and nondepressed people completed a Stroop task while an EEG was recorded (Holmes and Pizzagalli, 2008). The researchers examined the brain's response to performance errors during the task. As we reviewed in [Chapter 11](#), the anterior cingulate cortex is involved in detecting errors, and it then alerts DLPFC regions so that the DLPFC can exert more top-down control over behavior. This study found that among nondepressed participants, cingulate activity after mistakes was highly correlated with subsequent activity in the DLPFC. In contrast, depressed patients showed a pronounced response to errors in the cingulate cortex, but this response was not correlated with activity in the DLPFC in the same way as in control participants. In other words, although the system that normally detects errors was intact, its connection with regions that would permit subsequent adaptive changes in behavior was disrupted. This disruption in the functional connectivity between cingulate and DLPFC regions may explain why depressed people are unable to respond adaptively to performance errors or negative feedback, even when they are able to process the feedback itself.

Frontal lobe control systems are also important in emotion regulation, as we reviewed in [Chapter 12](#). In one study, patients with depression and matched nondepressed participants viewed upsetting pictures and were either told to experience

emotions naturally or told to attempt to view the pictures as a “neutral observer,” a form of emotion regulation involving cognitive reappraisal (Erk et al., [2010](#)). During the emotion regulation condition, depressed participants did not show the increase in activity in DLPFC that was present in control participants (see [Figure 14.9A](#)). Depressed participants also showed less functional connectivity between the amygdala and DLPFC, compared to controls, during active emotion regulation (see [Figure 14.9B](#)). About 15 minutes later, participants viewed the same pictures again without any specific instructions. In control participants, amygdala activation was reduced while viewing negative pictures for which they had previously practiced emotional regulation, whereas that evidence of emotion regulation was not evident in the depressed participants ([Figure 14.9C](#)). Together the results imply that in people with depression, top-down control mechanisms may not be engaged as they should be during attempts to regulate emotion.

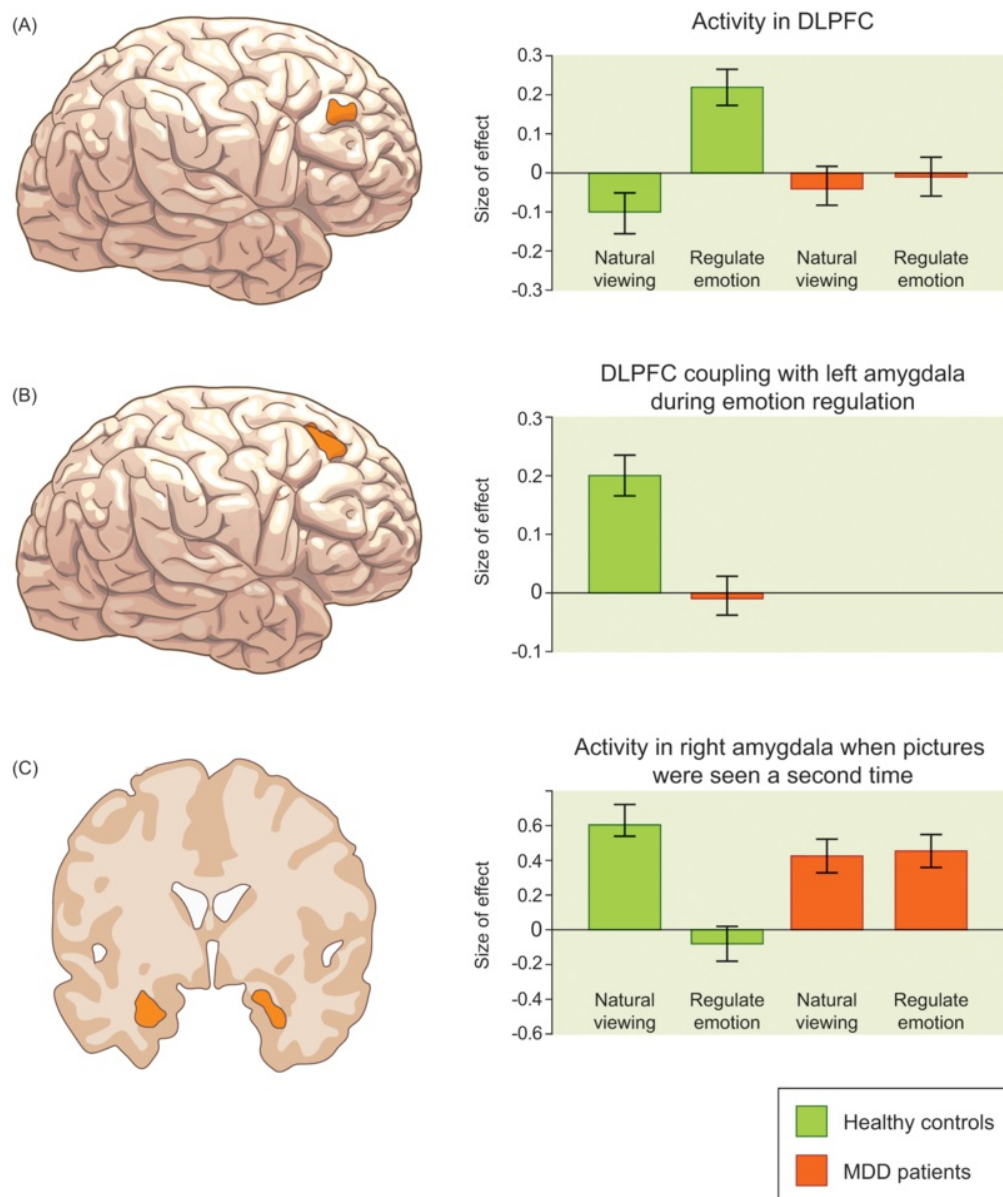


Figure 14.9 Disruption of neural activity during emotion regulation in depressed participants.

Patients with major depressive disorder (MDD) were compared to control participants during a task in which they viewed unpleasant pictures and were instructed to either view the pictures naturally or to cognitively reappraise the pictures in more neutral terms. For control participants, the instruction to regulate emotions led to increased activity in the DLPFC, but this pattern was not evident in the MDD participants (panel A). Furthermore, during active emotion regulation, control participants showed heightened functional connectivity between the DLPFC and the amygdala, a pattern that was absent in the MDD group (panel B). Finally,

activity in the amygdala during a subsequent viewing task was reduced for those pictures that had been previously cognitively reappraised, compared to those that had been naturally viewed, for the control group only; the effects of prior emotional regulation upon subsequent amygdala response to the pictures was absent in the MDD group (panel C).

(from Erk et al., [2010](#))

Another aspect of frontal lobe functioning that has been consistently related to depression involves hemispheric asymmetries of brain activation. Using EEG methods that measure activity in resting states, numerous studies have demonstrated greater right than left frontal activity among depressed participants (Davidson et al., [2002](#); Thibodeau et al., [2006](#)). For example, people with depression exhibit reduced activity in the left frontal region when anticipating a reward, implying a failure to engage the approach system that is indexed by left-hemisphere activity (Shankman et al., [2007](#)). Moreover, right-greater-than-left frontal activity is consistently observed among people who are at risk for a depressive episode, such as adolescents with a family history of depression or infants of depressed mothers (Dawson et al., [2001](#); Diego et al., [2004](#); Tomarken et al., [2004](#)). These findings indicate that asymmetric activation of frontal regions, as measured with EEG, may be a marker of susceptibility to depression.

An additional frontal region has been implicated specifically in treatment-resistant depression, that is, depression that does not improve following standard treatments. The relevant region is the subgenual region of the anterior cingulate cortex, illustrated in [Figure 14.10](#). This region is highly interconnected with other regions involved in emotion, such as the hypothalamus, which controls the body's stress responses, and the insula, which represents bodily states. Dysregulation in the subgenual cingulate cortex may be especially related to the somatic and vegetative symptoms of depression. High activity in this region in a resting state in someone with depressive symptoms appears to predict poor response to typical treatments for depression, prompting the search for alternative treatments (Dunlop and Mayberg, [2014](#)). Such findings indicate the potential

for cognitive neuroscience approaches to identify participants who would benefit from particular kinds of treatment based on pre-treatment brain activity.

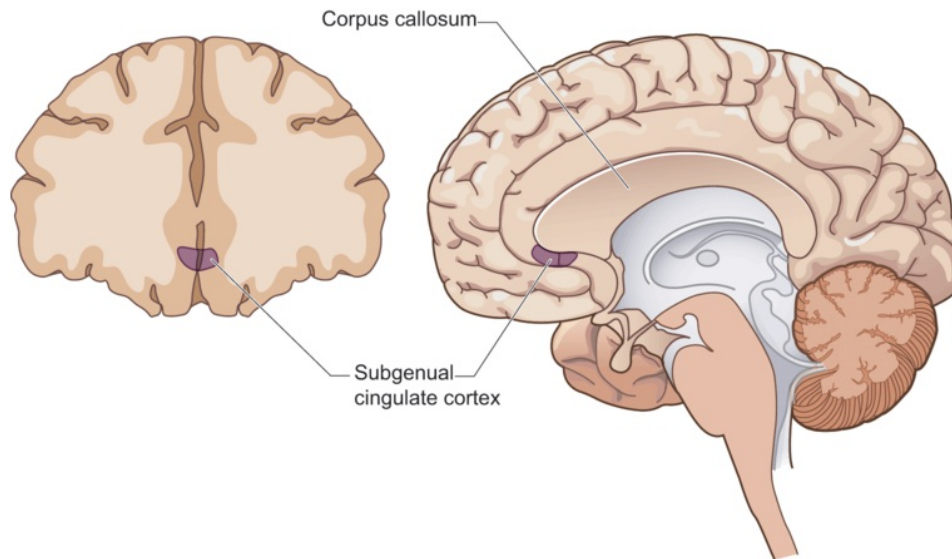


Figure 14.10 Subgenual region of the prefrontal cortex that is implicated in depression.

This region shows increased activity in depressed compared to nondepressed people. Furthermore, activity in this region decreases when therapeutic interventions, such as antidepressant drugs or electroconvulsive therapy, are effective.

Posterior Cortical Regions

In addition to the frontal lobes, posterior parts of the cortex, especially in the right hemisphere, are affected by depression (Levin et al., [2007](#)). As already mentioned earlier in this chapter, cognitive deficits in depression include difficulties on tasks of spatial function, implicating the right hemisphere. In addition, reduced activity in the posterior right hemisphere could contribute to the lethargy and fatigue seen in depression, as this region is thought to play a role in maintaining levels of arousal and vigilance (Heller et al., [2003](#)).

Evidence of reduced activation of right posterior areas in people with depression comes from several sources. EEG studies indicate that activity over the right parietal region is reduced in depressed participants during a resting baseline state and while

performing visuospatial activities such as dot localization and line orientation tasks (Kentgen et al., [2000](#); Rabe et al., [2005](#)). Multigenerational studies have also demonstrated reduced right parietal activity in individuals who are at risk for depression based upon a history of depression among their parents and grandparents (Bruder et al., [2005](#), [2007](#)). These latter studies imply that lower activity in this region may reflect a vulnerability factor that predicts susceptibility to depression. Finally, studies using event-related potentials have demonstrated that the N170 response to faces was reduced in depressed patients compared to controls; the group difference was especially evident over the right parietal region and for happy faces (Deldin et al., [2000](#)). Altered perception or memory for happy faces could contribute to the difficulties in interpersonal interaction that characterize depression (Deveney and Deldin, [2004](#)).

Functional Connectivity Among Cortical Regions

The brain's default mode network is hypothesized to contribute to internally generated thoughts about the self that often occur in resting baseline states, when participants are not directed toward a specific cognitive task. Because depression is often characterized by excessive self-focus and rumination, it seems plausible that default mode activation could be altered in depression. Indeed, a meta-analysis found that among people with depression, default mode network regions had an abnormally strong functional connection with the subgenual frontal cortex, which in turn is implicated in withdrawal-related emotional processes (Hamilton et al., [2015](#)). The strong pairing of self-referential thought with negative emotional content could contribute to the phenomenon of rumination observed in people with depression.

Another meta-analysis found disruptions in functional connectivity within frontoparietal networks for cognitive control among people with depression (Kaiser et al., 2015b). Specifically, depressed participants exhibited reduced functional connections between subregions of frontal and parietal cortex that are important in maintaining control over the focus of attention. These findings fit with the notion that cognitive control, particularly in the face of negative emotional distractions, is not

operating effectively in people with depression (see also Kaiser et al., [2015a](#)). Taken together, the findings from functional connectivity studies in depression remind us that a fuller understanding of the condition will emerge when we consider interactions among brain regions, rather than just activation within specific regions considered in isolation.

Subcortical Regions

Although many cognitive neuroscience studies of depression have focused on cortical regions, other studies have pinpointed abnormalities in subcortical systems as well. In particular, the amygdala appears to be overactive in depression, especially in response to negative information, whereas subcortical reward pathways are underactive in response to positive information. In addition, some evidence points to alterations in the hippocampal system as well.

As we have learned, the amygdala is involved in the processing of negative or threatening information as well as in learning the emotional significance of information. Thus, it should not surprise you that the amygdala might be affected in depressed people, who tend to see the world in a more negative light. The amygdala is more active among depressed individuals compared to control groups, even when activity is assessed during resting states (Davidson et al., [2002](#); Phillips et al., [2003](#)). Moreover, once amygdala activity is stimulated, the activity level does not subside as quickly in depressed people as in controls. For example, after presentation of a negative word, the amygdala stays active for longer in depressed people compared to controls (Siegle et al., [2007](#)). Amygdala activity is especially heightened in depressed people during the encoding of negative information into memory, which may account for the persistence of negative memories in depression (Hamilton and Gotlib, [2008](#)). As we reviewed previously, evidence suggests that the amygdala is not as tightly regulated by frontal lobe control regions in people with depression. These findings are consistent with other evidence that depressed people have difficulty disengaging attention from negative information, which can reinforce their negative mood states.

Because depression is characterized by an inability to find any pleasure in life – a characteristic termed **anhedonia** – you might expect that people with depression would have reduced activity in the subcortical reward pathways of the brain, such as the nucleus accumbens and related regions of the ventral striatum (Russo and Nestler, [2013](#)). Related dopaminergic motor systems, such as the basal ganglia, may also be implicated in the psychomotor slowing that is characteristic of depressed people. Animal models support the possible involvement of these brain systems in depression. For example, rats who exhibit helpless or anhedonic behavior (lack of interest in food, sugar water, or sex, for example) following a stressor tend to show altered spine density and neural firing within the ventral striatum (Russo and Nestler, [2013](#)).

Numerous studies have found reduced activity in the reward system in people diagnosed with depression (Whitton et al., [2015](#)). For example, one study found that among depressed people with higher levels of anhedonia, the ventral striatum was less active while viewing happy faces and generating memories of positive events (Keedwell et al., [2005](#)). People with depression, or those who are identified as at risk for depression, also show reduced ERP and ventral striatum responses to rewarding feedback in simple guessing games (Proudfit, [2015](#)). Because the reward pathway is one of the brain's major motivational systems, failure to activate this pathway could contribute to the apathy and lack of motivation seen in people who are depressed or at risk for developing depression.

Another limbic region that has been associated with depression is the hippocampus. You might be surprised that this structure is implicated in depression, because the hippocampus is often associated with memory. However, as we learned in [Chapter 12](#), the hippocampus works in conjunction with the amygdala to provide the context for learning emotional associations. Further, stress hormones are often elevated in depressed compared to nondepressed people, particularly following a stressor (Burke et al., [2005](#)), and these hormones are known to have a detrimental effect on the structure and function of the hippocampus (McEwen, [2009](#)). Indeed, anatomical studies indicate

that the size of the hippocampus is reduced in people with depression (e.g., Videbech and Ravnkilde, [2004](#)), and functional imaging studies have found underactivation of the hippocampus during the encoding of positive words in people with depression (van Tol et al., [2012](#)).

Interest in the role of the hippocampus in depression also increased when researchers discovered that the hippocampus is a major site for neurogenesis, the generation of new nerve cells, in adulthood (Christian et al., [2014](#)). Some researchers argue that the inability to generate new cells in the hippocampus may contribute to the origin or maintenance of depression (Duman, [2004](#); Jacobs, [2004](#); Mahar et al., [2014](#)), although this hypothesis remains controversial (Sahay and Hen, [2007](#)).

Therapeutic Interventions

Treatment for depression typically involves intervention at either the cognitive or the biological level, or both in combination. Cognitive therapy consists of identifying self-defeating and pessimistic thought patterns in depression and trying to alter those ways of thinking. Biologically based interventions often involve treatment with medication. Both cognitive therapy and antidepressant medication are relatively effective in treating depression in many people (Kamenov et al., [2017](#)). In addition, treatment methods based on noninvasive stimulation of the brain have been developed in recent years. In the following sections, we review what is known about the neural mechanisms involved in the treatment of depression and consider novel treatments that have been developed based on cognitive neuroscience findings.

How Standard Treatments for Depression Affect the Brain

Depression is often treated with drugs that affect the monoamine neurotransmitter systems of the brain (see [Chapter 1](#)). Typical drug treatments include serotonin-selective reuptake inhibitors (SSRIs), such as fluoxetine (Prozac) and escitalopram (Lexapro), which target the serotonin systems that are spread throughout the brain. Some other

antidepressant drugs affect other monoamine neurotransmitter systems, such as the norepinephrine and dopamine systems (Iosifescu et al., [2013](#)).

Although these drugs are well characterized at the molecular level – meaning that their immediate effects on the synapse are well understood – it is not yet clear exactly how or why they make depressive symptoms better. One possibility is that they restore a normal balance of neurotransmitter function through long-term changes in receptor sensitivity (e.g., Duman, [2009](#)). Another proposal is that these drugs may produce their therapeutic action by stimulating neurogenesis or other aspects of nerve cell growth (e.g., Hill et al., [2015](#); Sahay and Hen, [2007](#); Santarelli et al., [2003](#)). Regardless of the precise mechanism of action at the cellular level, neuroimaging studies indicate that pharmacological treatment of depression tends to reduce the response of the amygdala to negative information, while increasing prefrontal cortex responses (Wessa and Lois, [2015](#)).

A cognitive neuroscience framework may help to bridge the gap between biochemical and psychological models of depression. For example, [Figure 14.11](#) presents an integrated model of depression that incorporates many levels of analysis, from neurochemical through cognitive features, and also illustrates the possible points of intervention targeted by pharmacological therapy and cognitive therapy (Roiser et al., [2012](#)). According to this model, antidepressant drugs may work by influencing relatively low-level neural systems that create biases toward negative (unpleasant or threatening) stimuli in the environment (such as unfriendly faces or negative words), whereas cognitive therapies may work to address higher-level mental schemas or belief systems that are known to be maladaptive in depression (such as the depressed person's belief that things will never get better or that he or she is generally inadequate). Although there is still much to be worked out in such a model, it moves away from an “either/or” conception of drug versus cognitive therapy and allows for the possibility that both are effective through somewhat different neurocognitive mechanisms.

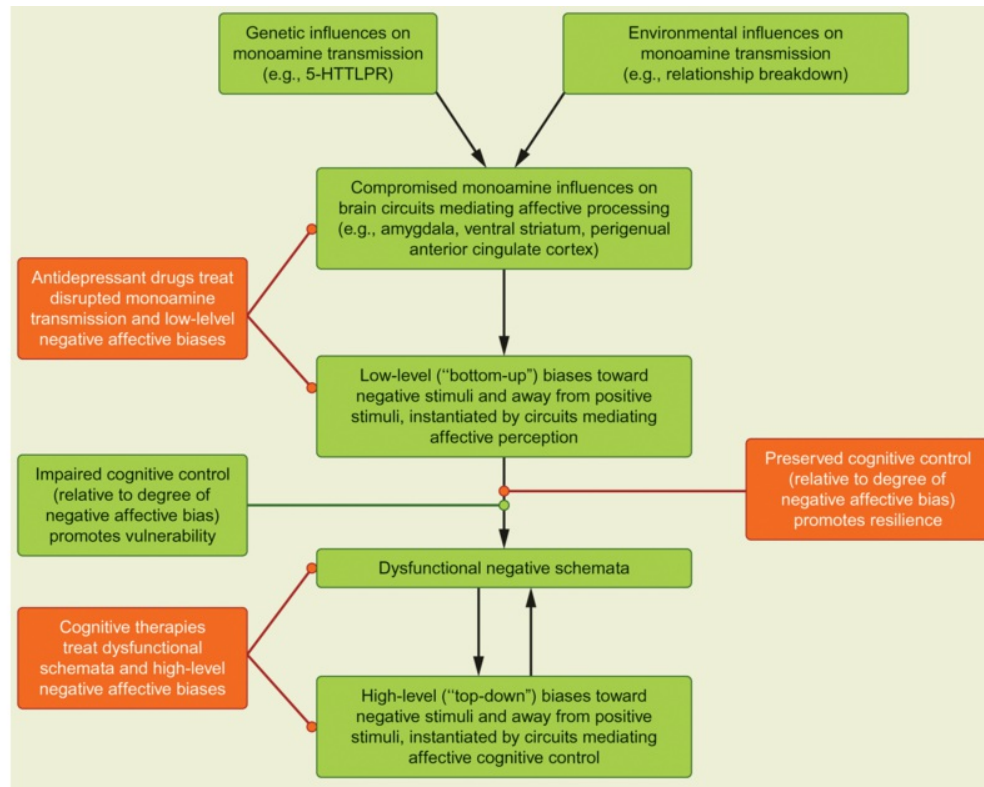


Figure 14.11 An integrated model of depression.

Green boxes indicate factors that increase vulnerability to depression, and orange boxes indicate factors, including treatments, that increase resilience against depression.

(from Rosier et al., [2012](#))

An exciting area of current research involves using imaging methods, and other biological markers, to identify which people exhibiting symptoms of depression are most likely to respond well to treatment. Knowledge gained in this area could ultimately have significant benefits, as physicians and psychologists could target specific drug or psychological treatments to the patients most likely to benefit from them, rather than using a “trial-and-error” approach to choose between possible treatments for individual patients. Some research suggests that brain imaging methods may be useful in this regard. For example, a recent meta-analysis found that people with higher baseline levels of activity in the anterior cingulate cortex were more likely to show clinical improvement with traditional drug or psychotherapeutic treatments for depression (Fu et

al., [2013](#)). Conversely, the same study found that participants with higher baseline activity in the insula and striatum were less likely to respond well to such treatment. Although our knowledge in this area is still incomplete due to limitations in existing studies (Phillips et al., [2015](#)), the possibility of individually tailored treatment approaches based on patterns of brain activity is a promising avenue for future research.

Noninvasive Stimulation Treatments

Despite the fact that medication and cognitive therapy can be effective treatments, as many as 50% of people with depression do not show significant symptom improvement with these treatments (Berton and Nestler, [2006](#)). Given the high prevalence of depression, the large number of people who do not respond to standard treatments, and the high risk of suicide among those who are not successfully treated, there has been great pressure to develop new treatments.

Among recent experimental treatments, [repetitive transcranial magnetic stimulation \(rTMS\)](#) is the least invasive and most well researched. In the United States, rTMS was approved by the FDA for treatment of depression in 2008. The procedure involves applying repetitive magnetic pulses to the brain from a generator that is held outside the scalp ([Figure 14.12A](#); see [Chapter 3](#) for a review of the TMS method). rTMS is conceptually similar to electroconvulsive therapy (ECT), in which electrical current is used to stimulate the brain. However, unlike ECT, rTMS does not induce seizures. As we've already noted, activity in the left prefrontal cortex appears to be underactive in depressed people; therefore, rTMS has been targeted to stimulate this region in most of the studies carried out so far.

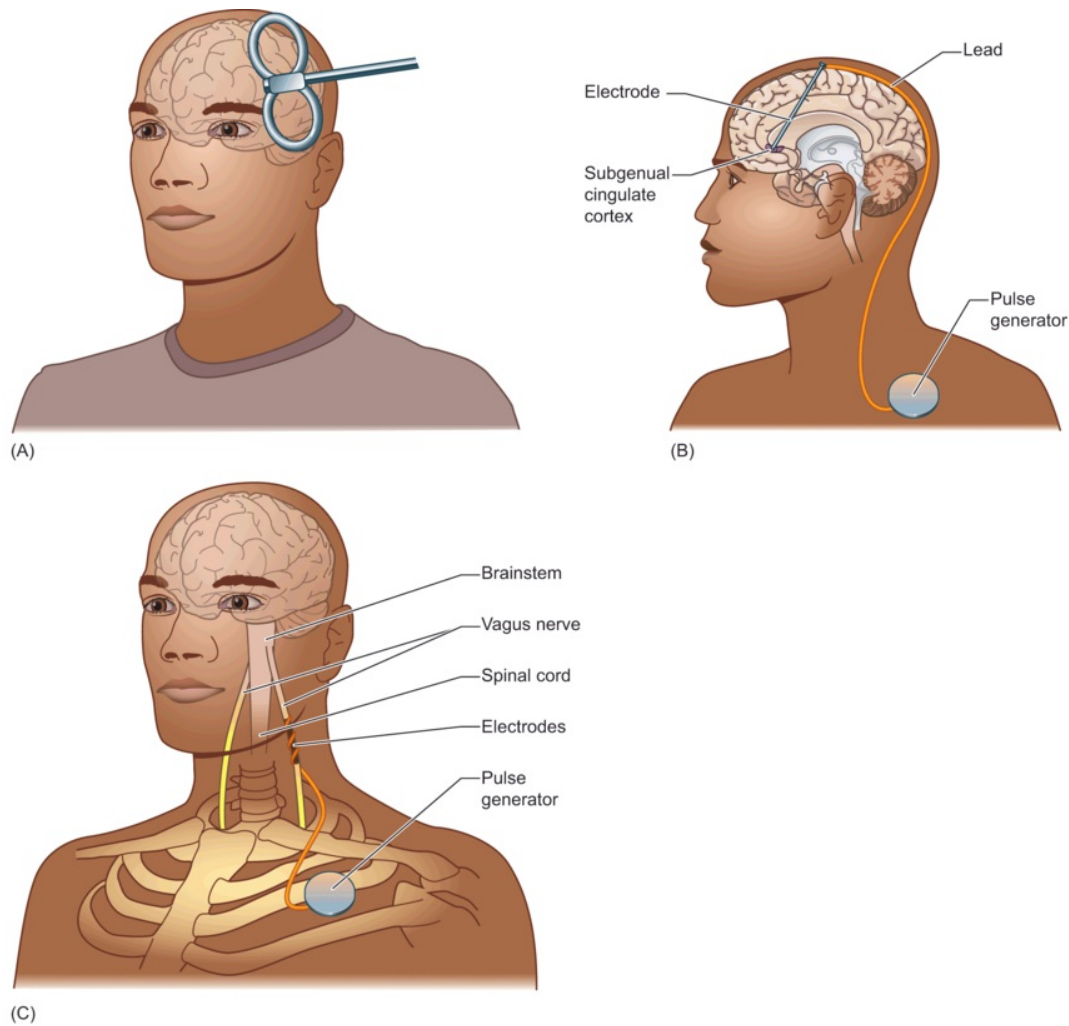


Figure 14.12 Some novel treatments for depression.

(A) Repetitive transcranial magnetic stimulation is a noninvasive procedure that involves placing a magnetic coil over the left dorsolateral prefrontal cortex to alter activity of the brain below the coil. (B) Deep brain stimulation is an invasive procedure in which the subgenual anterior cingulate cortex is stimulated by electrodes placed within the brain. (C) Vagus nerve stimulation is a procedure in which a device placed inside the chest cavity stimulates the vagus nerve as it enters the brain.

Numerous studies have found that rTMS is effective for treating depression (see Teng et al., [2017](#), for a meta-analysis). For example, in one study (Avery et al., [2006](#)), people whose depression could not be treated successfully with medication were randomly assigned to receive either rTMS or a sham procedure. The rTMS protocol

involved 15 sessions spread over a four-week period. Participants in the active treatment group received stimulation over the left dorsolateral prefrontal cortex in each session. Those in the sham control group attended the same number of sessions and also had the magnetic coil positioned over the left frontal cortex; however, the coil was positioned at an angle that would not actually stimulate the brain. After the 15 sessions, researchers found that about 30% of the rTMS-treated participants showed significant symptom reduction (symptoms reduced by at least half) on a rating scale, whereas only 5% of the sham-treated group showed such improvement. Other research with depressed participants has found improved quality of life after 24 weeks of treatment with rTMS, compared to a control group treated with sham TMS (Solvason et al., [2014](#)).

So, what possible mechanism explains how TMS might work to treat depression? TMS is assumed to affect the activity of underlying brain tissue, though it can do so either by interfering with processing by that brain region or by stimulating processing in that brain region. High-frequency TMS is thought to increase brain activity, whereas low-frequency TMS decreases it (Speer et al., [2000](#)). Thus, the underactivation of left compared to right prefrontal regions in depression could be ameliorated either by boosting the activity of left prefrontal regions or by reducing the activity of right prefrontal regions. High-frequency rTMS over the left dorsolateral prefrontal cortex (which most studies have used) increases activity in the dorsolateral prefrontal cortex and anterior cingulate regions (Kito et al., [2008](#)) and increases the release of the neurotransmitter dopamine in the caudate nucleus (Strafella et al., [2001](#)).

Further investigations are also exploring other targets within the frontal lobe, including dorsomedial and ventrolateral prefrontal cortex, in an effort to determine which region holds the most promise for beneficial effects when stimulated (Downar and Daskalakis, [2013](#); Fox et al., [2012](#)). More recently, tDCS, which is conceptually similar to TMS except relying upon electrical stimulation, has also been studied for effectiveness in treating depression, although results across studies are still inconsistent (Brunoni et al., [2016](#); Palm et al., [2016](#)).

Although it might seem surprising that doctors would use a treatment without fully understanding why it works, this situation is not unusual in psychiatry (or medicine more generally). For example, you have probably taken an aspirin for fever or for pain relief, yet the mechanism by which it relieves pain is not well understood; similarly, the mechanism by which rTMS can influence mental functioning is also not fully understood. The overwhelming complexity of the brain, coupled with the pressing need for effective treatments, means that use of treatments often precedes complete knowledge of their mechanisms of action.

Invasive Stimulation Treatments

Deep Brain Stimulation

A more invasive experimental treatment for severe depression is [deep brain stimulation \(DBS\)](#). This treatment involves the implantation of electrodes deep within the brain. Electrical current is then administered to modulate activity in the targeted brain region (see [Figure 14.12B](#)). DBS is used with some regularity to treat Parkinson's disease, a movement disorder (Hardesty and Sackeim, [2007](#); see [Chapter 4](#)). Researchers have examined whether DBS targeted toward either the subgenual cingulate cortex or the nucleus accumbens might alleviate depression, given the postulated roles of these regions in the disorder (see Anderson et al., [2012](#), for review).

An initial study focusing on the subgenual cingulate cortex examined six patients with severe treatment-resistant depression (Mayberg et al., [2005](#)). After DBS to the subgenual cingulate, the symptoms of four of these patients improved. These improvements were accompanied by decreases in activity of subgenual regions. Although the number of participants was small, the study generated interest in the potential promise of this treatment. A follow-up study examined a larger sample of 20 patients (including the six patients from the prior study) (Lozano et al., [2008](#)). Approximately a year after the DBS procedure, 55% of the patients met criteria for “response,” which was defined as a 50% decrease in rated symptoms of depression.

Researchers have also targeted the nucleus accumbens, a subcortical brain region that plays an important role in reward motivation. As reviewed earlier, because depression is characterized by anhedonia, or absence of pleasure, it is logical to posit dysfunction within the reward pathways. Preliminary studies suggest that DBS targeted toward the nucleus accumbens (and the medial forebrain bundle, a fiber bundle that is connected to it) may have beneficial effects in treatment-resistant depression (Schlaepfer et al., [2014](#)).

Needless to say, implanting electrodes inside the brain is a risky procedure. Risks include complications from the surgery itself and the potential for seizures induced by the electrical current. For these reasons, it is likely that DBS will only be a treatment of last resort for patients with severe depression who have already exhausted other options. Furthermore, knowledge of the effectiveness of the procedure is still preliminary. Few studies to date have included control groups, in which patients are randomly assigned to placebo or sham-operated conditions instead of the active treatment condition. There are good reasons for not including such controls in initial tests of the intervention; for example, it is ethically questionable to administer a sham surgery. However, full evaluation of the success of the procedure will ultimately require the comparison of treatment groups with adequate control groups.

Vagus Nerve Stimulation

Like DBS, [vagus nerve stimulation \(VNS\)](#) involves stimulation of the nervous system, but in this case the stimulated structure is the vagus nerve. This nerve carries sensory information from the internal organs – stomach, intestines, heart – into the brain, as well as carrying motor information from the brain to these organs. Just as DBS was adapted from treatments used for Parkinson's disease, VNS was adapted from treatments used for epilepsy. In the VNS procedure, a device containing stimulating electrodes is implanted in the upper chest, near the collarbone, where it can stimulate the vagus nerve before it enters the brain (see [Figure 14.12C](#)). This implantation is less invasive than

DBS because the implantation does not penetrate the brain itself, but VNS still involves a surgical procedure and the presence of a foreign device inside the body.

Researchers using VNS to treat epilepsy noticed improvements in the mood of their patients. Building upon this finding, VNS became an experimental treatment for depression (Groves and Brown, [2005](#)). Initial studies found significant improvements in depressive symptoms over time in people treated with VNS (e.g., Marangell et al., [2002](#); Rush et al., [2000](#)). However, these studies did not directly compare VNS-treated people to untreated or sham-treated controls. A meta-analysis (sponsored by the device manufacturer) compared patients with chronic, treatment-resistant depression who were receiving “treatment as usual” (whatever psychotherapy or drug treatment the patient would normally receive) with similar patients who were receiving both “treatment as usual” and VNS combined. The study found better signs of improvement in the patients with the VNS added (Berry et al., [2013](#)). Thus, evidence for the effectiveness of VNS is accumulating, although inconsistencies across studies persist (Martin and Martin-Sanchez, [2012](#)).

How might VNS work to treat depression? At least two possibilities have been proposed, the first focusing on monoamine neurotransmitters and the second focusing on neural plasticity (Grimonprez et al., [2015](#)). The vagus nerve, coming from the chest cavity, terminates in a brainstem structure known as the nucleus of the solitary tract. The nucleus of the solitary tract projects to the locus coeruleus (also in the brainstem), which is the major source of noradrenergic projections throughout the brain. Therefore, stimulation of the vagus nerve can influence the activity of noradrenaline, a monoamine neurotransmitter associated with arousal and alertness (see [Chapter 1](#)). Through this pathway, VNS might act to ameliorate the states of low arousal that are typical in depression. In addition, the nucleus of the solitary tract also connects to limbic structures, projecting directly to the amygdala and indirectly to the hippocampus. VNS may facilitate aspects of neural plasticity, including neurogenesis and synapse production, particularly in the hippocampus (Grimonprez et al., [2015](#)). As with DBS,

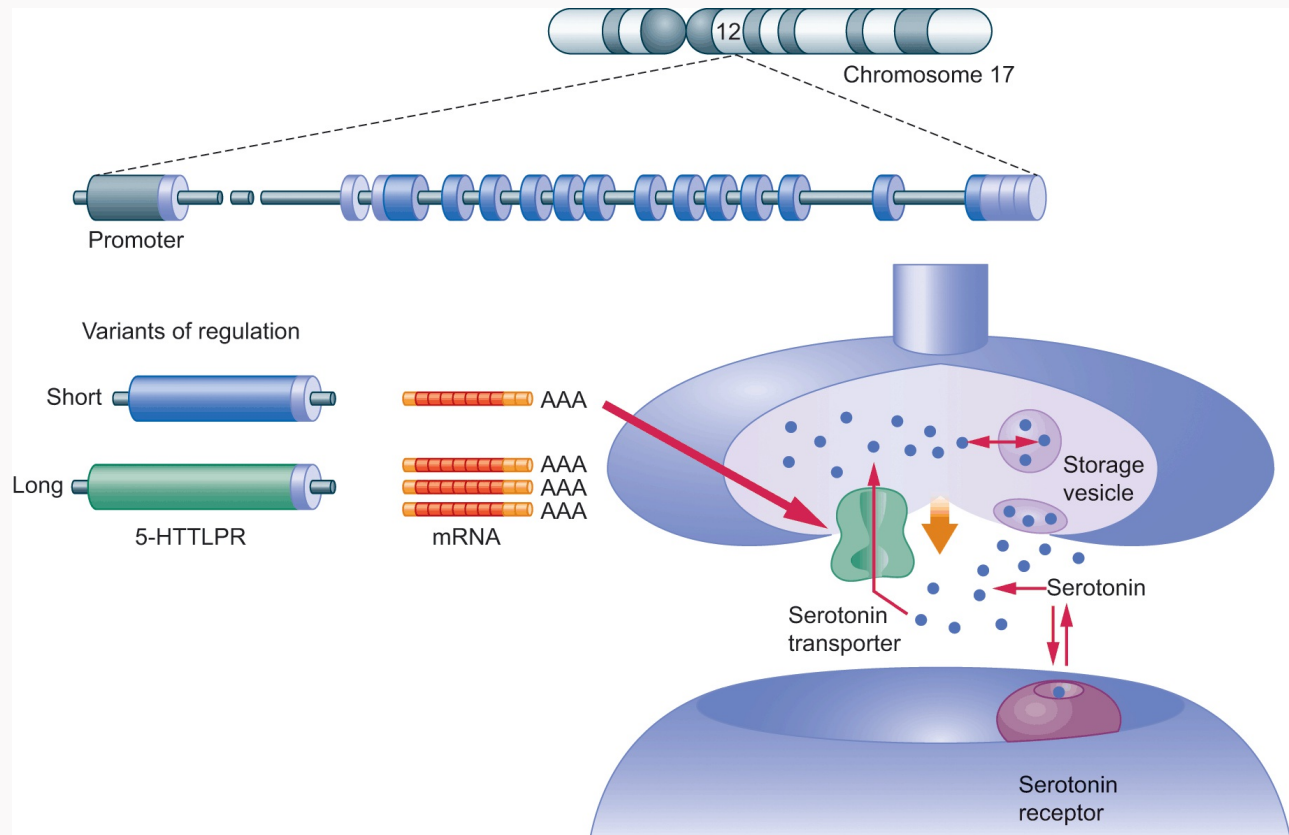
studies of the effectiveness of VNS have preceded a full understanding of its mechanism of action.

In Focus: Can Your Genes Make You Unhappy?

Researchers have long been interested in the question of whether some people's genetic make-up predisposes them to be melancholy, pessimistic, or prone to worry or fear. Though results from twin studies imply that nearly every psychological trait, including personality traits and psychopathology, has a heritable component, twin studies cannot tell us which specific genes might play a role in mood disorders. With the recent advent of molecular genetics, such questions can now be addressed. Individual genotypes can be assessed from a simple cheek swab, in which cells from the inside of the cheek are collected with a cotton swab and DNA is extracted from the cells. Researchers can then try to determine whether possession of a particular variant of a gene is associated with certain psychological traits.

One of the best-studied genes related to emotion and mood disorders is the [serotonin transporter gene](#) (this gene is also known as the 5-HTT gene, because serotonin is often abbreviated as 5-HT). This gene codes for the serotonin reuptake protein, which takes the neurotransmitter serotonin from the synapse back up into the presynaptic cell (see [Box Figure 14.1](#)). Because we know that the serotonin system is implicated in depression – most antidepressant drugs are known to affect serotonin neurotransmission – it makes sense that individual differences in this particular gene could be relevant to mood disorders. There are two main variants of this gene, the so-called long allele (L) and the short allele (S). Because every person gets one copy (allele) of a gene from his or her father and one copy from his or her mother, any person can have one of three possible genotypes: L/L, S/S, or S/L. These genotypes are all fairly common in human populations; that is, they are all normal variations. Variations

in this gene have been related in a surprising number of ways to psychological traits, cognition, and brain activity (Canli and Lesch, [2007](#); Hariri and Holmes, [2006](#)).



BOX Figure 14.1 Individual differences in the gene that codes for the serotonin transporter molecule.

This gene is located on chromosome 17, and a specific subregion of the gene, the promoter region, comes in either a “short” or a “long” variant. Compared to a long variant, a short variant results in less of the serotonin transporter molecule in the synapse and is associated with increased fear and anxiety.

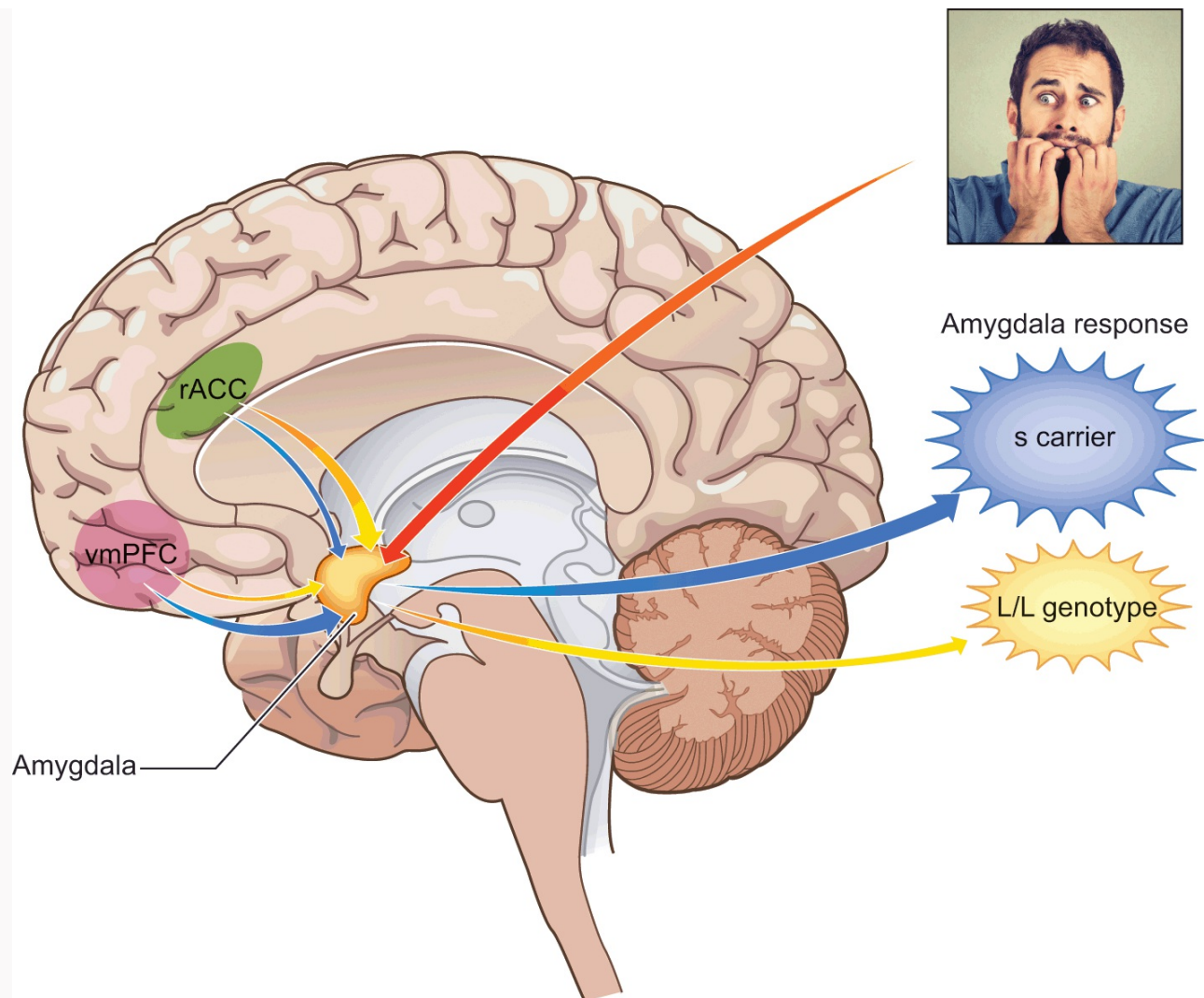
(from Canli and Lesch, [2007](#))

Initial studies linked individual differences in the serotonin transporter gene with self-reported measures of anxiety and mood, finding that those with one or two S alleles tended to report higher levels of neuroticism, anxiety, hostility, depression, worry, and pessimism (e.g., Greenberg et al., [2000](#); Lesch et al.,

[1996](#)). Subsequent research showed that people with at least one S allele were faster to acquire fear responses in a classical conditioning paradigm in which a previously neutral image, like a picture of a circle or triangle, was repeatedly paired with a mild shock (Garpenstrand et al., [2001](#)). People with this genotype also show different patterns of attention to emotional information. Whereas those with the L/L genotype tend to shift their attention away from emotionally threatening words, those with the S/S or S/L genotype tend to shift their attention toward emotionally threatening words (Beevers et al., [2007](#)). These studies show that genotype influences emotional learning and attention, as well as correlating with self-reported personality traits.

Does the brain process information differently in people depending on their genotype? Given that people with an S allele seem to acquire fears faster, we would expect them to show heightened activity in the amygdala, which is responsible for fear learning. Indeed, some researchers have found greater amygdala activity in response to fear stimuli relative to neutral stimuli among those with an S allele (S/S or S/L genotype) compared to those with the L/L genotype (Hariri et al., [2002](#); though see Murphy et al., [2013](#), for inconsistent findings). Another study found evidence that the amygdala may be more poorly regulated by the frontal lobes in those with an S allele (Pezawas et al., [2005](#); see also Volman et al., [2013](#)). In this study, people with the L/L genotype tended to have a pattern of brain activity in which higher activity in the anterior cingulate was strongly associated with lower activity in the amygdala. This relationship was weakened in those with an S allele, implying that the cingulate had less tight control over the amygdala in individuals with the S allele. At the same time, a related study found increased coupling between amygdala and ventromedial prefrontal activity among those with the S allele (Heinz et al., [2005](#)). Thus, in those with the S allele, the amygdala's activity may be more driven by the emotion-related ventromedial frontal cortex and, at the same time, be less

influenced by cognitive control structures of the frontal lobe (see [Box Figure 14.2](#)).



BOX Figure 14.2 Possible differences in interregion connectivity associated with serotonin transporter genotype.

The amygdala's response to a fearful face is stronger among those who are carriers of the S allele (S/S or S/L genotype) compared to those with the L/L genotype. One possible reason for this genotype difference is that the L/L genotype may be characterized by greater top-down control over the amygdala by the rostral anterior cingulate cortex (rACC). This difference in top-down control is depicted by the larger arrow from the rACC to the amygdala for the L/L group (yellow arrow) compared to the S carriers (blue arrow). In contrast, the amygdala may be more activated by the ventromedial prefrontal cortex (vmPFC) in S carriers compared to those with the L/L genotype.

(from Hamann, [2005](#))

Given all of these findings, it stands to reason that individuals with an S allele might be more prone to developing clinical depression or an anxiety disorder than those with the L/L genotype (Hoefgen et al., [2005](#)). However, there is a wrinkle: Evidence indicates that it may not be the mere presence of one of these genotypes alone that best predicts clinical symptoms, but rather the interaction of these genotypes with life stressors. In a landmark study, researchers collected both genotype information and measures of life stressors over a six-year period, and used those variables to predict depressive symptoms at the end of the six years (Caspi et al., [2003](#)). Results revealed that those people who had the combination of a high number of life stressors and the S/S genotype were most likely to show high levels of depressive symptoms. The presence of an S/S genotype in a person with low levels of stress was not associated with depression. These results are an excellent demonstration of [gene-environment interactions](#). A particular outcome – in this case, depression – can be predicted only when both genetic and environmental factors are taken into account. Complicating this picture, however, subsequent studies have not been able to consistently replicate this key interaction between genotype and life stress in predicting depressive symptoms (Lester et al., 2017).

Other studies also suggest a more complex relationship between 5-HTT genotype, environmental factors, and emotional well-being. For example, one study examined genotype effects in a sample of children from a Romanian orphanage who had been randomly assigned, as part of the study, either to high-quality foster care or to continued orphanage rearing (Brett et al., [2015](#)). The environment of rearing – foster care versus orphanage care – had a much bigger impact for those children with the S/S genotype. Interestingly, these S/S children showed more externalizing (“acting out”) behavior than other genotypes when raised in the orphanage, but less externalizing behavior than other genotypes when raised in a high-quality foster-care family. This result suggests that the S/S

genotype confers “differential susceptibility,” or increased sensitivity to the quality of the caregiving environment in both positive and negative directions.

Recent work on 5-HTT genotype differences has also begun to take into account the role of epigenetics. Epigenetics, literally meaning “on top of the genes” or “in addition to genes,” refers to the impact of external factors upon DNA transcription. Epigenetic factors do not change the DNA sequence itself, but they change how the genes are expressed. One study found that activity in the amygdala in response to threatening stimuli was driven not only by individual differences in 5-HTT genotype, but also by individual differences in epigenetic factors that affect that gene’s transcription (Nikolova et al., [2014](#)). Specifically, the degree of DNA methylation in this region of the genome was positively associated with increased amygdala reactivity to threatening images. The researchers speculate that greater methylation is associated with decreased expression of the serotonin transporter gene. While the mechanisms are still to be worked out, these results indicate that understanding the pathways among genes, brain activity, cognitive-emotional processing, and psychopathology will need to take into account individual differences in factors affecting gene expression, not just the genes themselves.

Thus, the question “Can your genes make you unhappy?” turns out not to have a simple answer. People with the S allele of the serotonin transporter gene appear to be more reactive to negative emotional information and are perhaps more likely to develop depression in response to serious life stressors, compared to people with L/L genotypes. However, there are important caveats. First, many people have a copy of the S allele – as much as 20% of the population has the S/S genotype, and roughly 50% of the population has the S/L genotype. Clearly, not all of these people are clinically depressed! Furthermore, early findings with regard to genotype and psychopathology have not always been consistently replicated. While a single gene may provide some predictive

information about a person's likelihood of responding negatively to stress, it is clearly not the sole determinant. In fact, any single gene is likely to have only a small impact on outcome measures related to psychopathology. Many other genes, epigenetic factors, and life experiences also interact in complex and as yet unknown ways to influence a person's resilience to the slings and arrows of life (see Gratten et al., [2014](#), for additional critical review).

Anxiety Disorders

Anxiety disorders are also very prevalent in the population; depending on demographic factors, 5–20% of the population will be affected by an anxiety disorder at any given time (Remes et al., [2016](#)). Like depression, anxiety disorders are more common among women than men. Furthermore, depression and anxiety are often comorbid, meaning that they tend to occur together in the same people (Kessler et al., [2005](#)). The comorbidity of anxiety and depression suggests that they have common origins. At the same time, this comorbidity often complicates research, because it is difficult to separate cognitive and neural characteristics that are associated uniquely with anxiety versus depression.

Symptoms and Features

Like schizophrenia and depression, anxiety is a heterogeneous syndrome. Anxiety plays a role in many different disorders, though all of the related clinical conditions share a preoccupation with nervousness and fear that interferes with daily life. There are two main ways of organizing all the variations of anxiety. First, we can consider separate diagnostic categories and their typical symptoms. Second, we can consider common dimensions that underlie many of the diagnostic categories, such as worry or panic.

The main diagnostic categories of anxiety disorders include phobias, panic disorder, posttraumatic stress disorder, generalized anxiety disorder, and obsessive-compulsive disorder. Although all of these conditions involve the experience of fear and anxiety, they differ in the object, cause, and manifestation of the fear. [Phobias](#) are fears centered

on specific objects or situations, such as spiders, snakes, heights, closed spaces, or social settings. To qualify as a phobia, a fear must be irrational and interfere with normal functioning. People with phobias often go to great lengths to avoid situations in which they may encounter the feared object, and they may panic when confronted with that object. In contrast, when a person has repeated panic attacks – which include sensations of extreme bodily hyperarousal, dizziness, shortness of breath, elevated heart rate, and sense of losing control – he or she is diagnosed with a [panic disorder](#). Panic disorder may be associated with fear of specific situations, such as being in a public space, but it need not be.

Whereas the origins of phobias and panic disorder may be uncertain, [posttraumatic stress disorder \(PTSD\)](#) has a clear origin: a deeply traumatic experience such as combat, rape, or survival of torture, natural disaster, or other life-threatening experience. Symptoms of PTSD include extremely vivid and intrusive recollections of the traumatic situation (e.g., nightmares), avoidance of situations related to that experience, chronically elevated bodily arousal, and feelings of survivor guilt and suicidal thoughts.

[Generalized anxiety disorder](#) involves a free-floating and chronic experience of anxiety. In this disorder, the anxiety is not tied to any specific triggering event or object, which makes it more difficult to address and treat. Finally, in [obsessive-compulsive disorder \(OCD\)](#), the afflicted person has obsessive thoughts about harm and, to cope with that anxiety, engages in repeated, compulsive actions intended to ward off a negative outcome. For example, a person obsessed with fear of contamination may wash his or her hands hundreds of times a day. Although OCD is no longer grouped with anxiety disorders in the current DSM-5 diagnostic scheme, we consider it together with other aspects of anxiety here due to some shared features.

As you can see, there are a variety of clinical problems related to anxiety, and each has unique as well as shared features. To emphasize some commonalities across different anxiety-related conditions, researchers have identified two main dimensions of anxiety: anxious apprehension and anxious arousal (e.g., Nitschke et al., [2000](#); Sharp et

al., 2015). [Anxious apprehension](#) refers to the nervous anticipation of something bad that could happen in the future; the one word that sums up anxious apprehension is “worry.” [Anxious arousal](#), in contrast, refers to a state of bodily and cognitive hyperarousal that corresponds with our usual sense of the word “panic.” Anxious arousal is characterized by physiological symptoms that indicate activation of the sympathetic nervous system, such as increased heart rate and sweaty palms.

Anxious apprehension and anxious arousal occur in different mixes in the various anxiety disorders. For example, in generalized anxiety disorder, worry dominates. During panic attacks, anxious arousal dominates; however, a person with panic disorder often develops worries about a potential panic attack. Likewise, someone with a phobia about public speaking may worry in advance about an upcoming class presentation, and he or she may experience anxious arousal (panic) at the time of the presentation. As we will see later, anxious apprehension and arousal appear to have different neural correlates.

Cognitively, the main feature of anxiety disorders is an exaggerated bias to pay attention to threatening information in the world (Armstrong and Olatunji, 2012; Cisler and Koster, 2010). This attentional bias has been demonstrated through various cognitive tasks. In the [emotional Stroop task](#), the person must identify the ink color of words. Anxious individuals are slower to name the ink color of emotionally threatening words, such as “kill,” than nonemotional words such as “sum,” implying that attention has been automatically captured by the word’s emotional meaning (see [Figure 14.13A](#)).

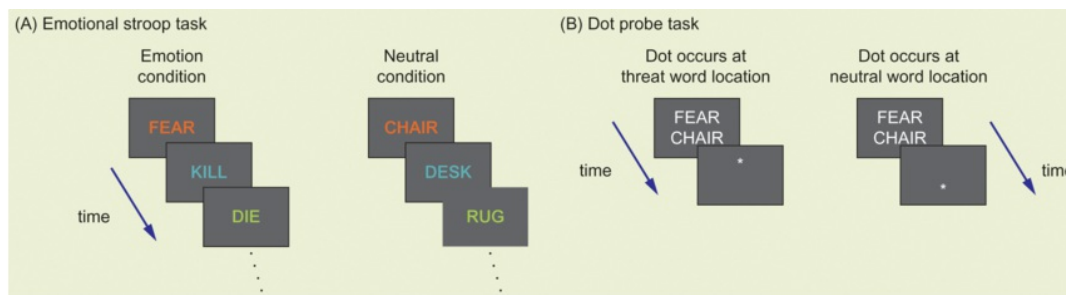


Figure 14.13 Cognitive tasks used to measure attentional biases in anxiety.

(A) Emotional Stroop task: The participant must identify the ink color while ignoring the word meaning. Anxious people are slower when the word is emotionally threatening (e.g., “fear”) than when it is neutral (e.g., “chair”). (B) Dot probe task: The participant must press a button as quickly as possible when a dot appears somewhere on the screen. The dot is preceded by two words, one threatening and one neutral. These words are irrelevant to the main task. However, anxious people will tend to respond more quickly to the dot when it appears at the same location where a threatening word had just been shown than when it appears at the location where the neutral word was shown, indicating that attention has been shifted to that threatening word.

Another task used to demonstrate attentional bias toward threatening information is the [dot probe task](#). In this task, the person simply has to indicate the presence of a dot that is flashed on the screen. The dot is preceded by a pair of words, one of which is emotionally threatening. Researchers compare the speed of response to the dot depending on whether it appears at the same or opposite location in relation to the threatening word (see [Figure 14.13B](#)). Participants who shift attention toward the emotional word will be faster to respond to the dot when it appears at that location. In these tasks and in others that are similar, anxious people tend to show an increased attentional focus on threatening information, especially if the information is associated with the specific object of their anxiety (e.g., the word “web” for people who have a phobia of spiders). Training to reduce attentional biases can help to reduce anxiety symptoms (Hakamata et al., [2010](#)), and individual differences in the degree of attentional bias can predict treatment outcome (Barry et al., [2015](#)).

Amygdala and Hippocampus

It should not be surprising that the amygdala is implicated in anxiety disorders. As we learned in [Chapter 12](#), the amygdala is crucial for the acquisition of learned fears, and it is well situated to provoke the body's fight-or-flight response to stimuli. This structure is also important in directing attention to stimuli that are especially emotionally salient or urgent, and for this reason it plays a role in threat-related attentional biases in anxiety.

Numerous studies have found that activity in the amygdala is increased when anxious individuals are confronted with their fear-inducing objects or situations (Etkin and Wager, [2007](#)). For example, the amygdala's activity is increased in people who have a social phobia (compared to control groups) when they view faces or are asked to make a public speech. Among social phobics who were treated with either anxiety-relieving drugs or cognitive therapy, improvement in symptoms was paralleled by decreases in amygdala activity during a public speaking task (Furmark et al., [2002](#)). Other research has found increased amygdala activity in combat-related PTSD patients viewing combat scenes or listening to combat-related sounds (Pissiota et al., [2002](#); Rauch et al., [1996](#); Shin et al., [1997](#)). The amygdala also appears to be more active in anxious compared to nonanxious people during situations of uncertainty, in which a threatening stimulus may or may not materialize (Grupe and Nitschke, [2013](#)).

Anxiety also influences the amygdala's sensitivity to threatening information that is presented outside the main focus of attention. In one study, participants viewed a display that included pairs of faces and pairs of houses (see [Figure 14.14A](#); Bishop et al., [2004b](#)). In one condition in the study, the participants made a decision about the houses while ignoring the faces; in the other condition, they made a decision about the faces while ignoring the houses. The expressions on the faces were sometimes fearful and sometimes neutral. Among participants with low self-reported levels of anxiety, the amygdala was responsive to the fearful faces only when the faces were the main focus of attention. However, for participants who reported high levels of anxiety, the

amygdala was responsive to the fearful faces even when they were outside the main focus of attention, that is, when the participant was supposed to be paying attention to the houses and ignoring the faces (see [Figure 14.14B](#)). These findings reflect the preferential processing of threatening information in anxious people, even when that information is not relevant to the task at hand.

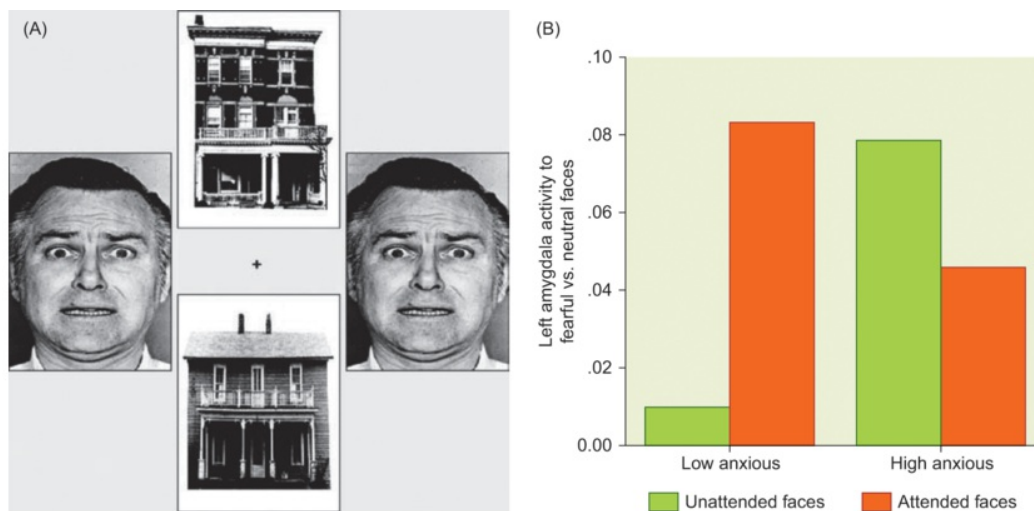


Figure 14.14 Anxiety affects amygdala response to unattended threats.

(A) Participants in this study viewed an array that included faces and houses. In some sets of trials, they were supposed to pay attention to the faces; in other sets, they were to pay attention to houses (from Bishop et al., [2004b](#)). (B) In low-anxious people, the amygdala showed greater response to fearful faces compared to neutral faces only when the participant was supposed to pay attention to the faces. In high-anxious people, the amygdala was responsive to the fearful faces even when the participant was supposed to ignore them.

The amygdala is also crucial in [extinction](#), the process by which acquired fears are later lost. Extinction is typically delayed or reduced in people with anxiety disorders, meaning that they have a harder time losing fear associations that have already been established (Duits et al., [2015](#)). Typically, extinction is studied in animal models by first training an animal to associate a particular stimulus with an aversive outcome, and then presenting the stimulus repeatedly without the aversive outcome and measuring how long it takes the animal to learn that the stimulus is now “safe.” Extinction learning in

animals depends upon the activity of NMDA receptors of glutamatergic neurons within the amygdala; when those receptors are blocked, extinction is eliminated (Davis et al., [2005](#)). Further, when NMDA receptors within the amygdala are stimulated, extinction is facilitated (Ledgerwood et al., [2003](#); Walker et al., [2002](#)). Treatment for anxiety disorders such as phobias and PTSD have long taken advantage of the process of extinction by gradually and repeatedly exposing the person to the feared situation or cues in a safe setting, so that over time the fear is lost or inhibited.

Although the amygdala is clearly involved in the emotional learning that plays a role in anxiety disorders, the hippocampus is also implicated, particularly in PTSD. Numerous studies have found smaller hippocampal volumes in combat veterans who have PTSD compared to control groups (Pitman et al., [2012](#)). The hippocampus is crucial in supporting aspects of memory encoding and consolidation (see [Chapter 9](#)), and some symptoms of PTSD, such as flashbacks, involve problems in controlling memory retrieval. Therefore, it is logical to consider whether deficient hippocampal functioning may contribute to symptoms of PTSD. One question that immediately arises is whether people with a smaller hippocampus prior to the trauma are less able to cope and therefore more likely to develop PTSD, or, alternatively, whether the trauma itself has a direct influence on the hippocampus that leads to the development of PTSD. The latter possibility is plausible because animal studies have shown that stress, through its effects on hormone levels, can have a damaging effect on the hippocampus (McEwen, [2009](#)).

To address whether hippocampal differences precede or follow the traumatic experience in PTSD, one group of researchers used a clever design involving identical twins (Gilbertson et al., [2002](#)). The participants in the sample were all identical twins in which one twin of each pair was exposed to combat and the other was not. Some of those who were in combat later developed PTSD, and some did not. Replicating other findings, veterans with PTSD showed a smaller hippocampus than those without. More interestingly, the identical twins of veterans with PTSD had smaller hippocampi than the twins of veterans without PTSD. Furthermore, identical twins tended to have similarly

sized hippocampi. These findings suggest that the small hippocampus seen in patients with PTSD may precede the trauma experience, rather than being a consequence of the trauma experience. Other research found that a smaller hippocampal volume in veterans with PTSD predicted a poorer treatment outcome, compared to veterans with PTSD whose hippocampus was larger (van Rooij et al., [2015](#)). Thus, a small hippocampus may be a vulnerability factor that makes some people more likely to develop the disorder when faced with an intense trauma, as well as more resistant to treatment.

Cortical Regions

Regulation of Anxiety

As we reviewed in [Chapter 12](#), one mechanism of regulating emotional experience involves exerting top-down control of frontal regions over subcortical emotion structures such as the amygdala. Therefore, the functioning of the frontal lobes, and particularly their relationship to subcortical structures, has been examined in anxious people, in whom fear responses do not seem to be well regulated. As we discuss next, the functioning of both medial and dorsolateral frontal regions is relevant to understanding anxiety.

In the [previous section](#), we discussed the role of the amygdala in fear extinction. However, the amygdala is not solely responsible for this process; regions of the medial prefrontal cortex contribute to extinction as well. Animal studies show that lesions in the medial prefrontal cortex can lead to an impairment in extinction, particularly in the ability to retain learned extinctions – the knowledge that a cue now signals a “safe” situation (Milad et al., [2006](#); Sotres-Bayon et al., [2004](#); see Calhoun and Tye, [2015](#), for review). [Figure 14.15](#) illustrates sample results from extinction learning in an animal study. A recent study in humans with surgical damage to the ventromedial prefrontal cortex found elevated amygdala responses to negative information, fitting with the animal studies in implying that medial prefrontal cortex normally regulates the amygdala’s reactivity (Motzkin et al., [2015](#)). Reduced activation of the ventromedial

prefrontal cortex in anxious people, such as patients with PTSD (Pitman et al., [2012](#)), may lead to difficulty in remembering that feared situations are actually safe.

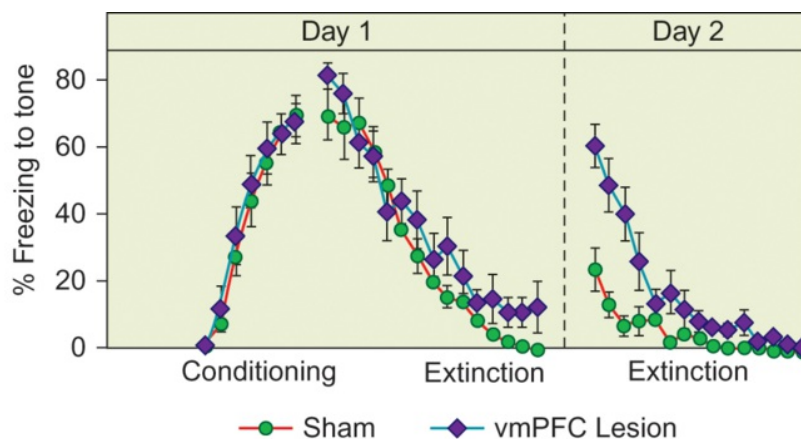


Figure 14.15 Effects of medial prefrontal lesions on extinction learning.

During the conditioning phase, the rat learns to associate a tone with a shock; freezing behavior to the tone (shown on the y axis) increases equally for sham-lesioned animals and those who received a lesion to the medial ventromedial prefrontal cortex (vmPFC) prior to conditioning. During the extinction phase, the tone is presented alone without the shock. As the number of trials without shock increases, freezing behavior to the tone decreases, slightly more for sham-lesioned than vmPFC-lesioned animals. More dramatically, however, rats with vmPFC lesions do not retain extinction learning from the first to the second day of testing to the same extent as sham-lesioned rats, and extinction must be relearned.

Source: Fig. 2 in Milad, M. R. et al. ([2006](#)). Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biological Psychology*, 73, 61–71.

Reprinted by permission of Elsevier.

Prefrontal–amygdala interactions may also contribute to the threat-related attentional bias that is characteristic of anxious people (Bishop, [2007](#)). One study provided evidence that frontal lobe regions may not exert as much top-down control in anxious individuals when distracting threatening information is present (Bishop et al., [2004a](#)). In this study, as threatening distractors became more frequent, activity in dorsolateral frontal regions tended to increase, presumably as part of a system of cognitive control.

However, this effect was reduced in people who reported high levels of anxiety. Highly anxious participants also had reduced activity in the rostral anterior cingulate cortex in this study. Together, the results suggest possible dysregulation of frontal lobe control systems in anxious people. Although the implications for treatment are not yet clear, one possibility is that cognitive training in controlling the focus of attention could benefit anxious people.

Monitoring and the Anterior Cingulate

Ventral portions of the anterior cingulate cortex have also been implicated in a number of different anxiety disorders, most likely due the role of this region in action monitoring (Koban and Pourtois, [2014](#)). As we've learned previously, activity in the anterior cingulate can serve to select actions and to send an important signal to other brain systems, indicating whether an action has led to a desired outcome (see [Chapter 11](#)).

As such, it may not surprise you, then, to learn that studies have found heightened activity in the anterior cingulate cortex among anxious people. For example, the error-related negativity, which represents activity in the cingulate cortex following errors, is elevated in patients with obsessive-compulsive disorder and in those who report high levels of worry (Gehring et al., [2000](#); Hajcak et al., [2003](#); Moser et al., [2013](#)). Neuroimaging studies have also found that the cingulate's activity is higher in people with anxiety disorders compared to control participants, both during resting conditions and when provoked by threatening stimuli (Kent and Rauch, [2009](#)). An overactive anterior cingulate region may reflect that the values of actions are given a heightened affective tag.

One of the most controversial therapies for intractable anxiety disorders is a surgical intervention in the cingulate region. A procedure called [cingulotomy](#) involves the intentional creation of bilateral lesions in the anterior cingulate. Needless to say, this procedure has generated much debate, because brain surgery is highly invasive and brain lesions are not reversible. Therefore, the procedure should never be used unless

the person's anxiety is so severe that daily functioning is impossible, and only when all other treatments have failed. Although some studies suggest potential benefits of cingulotomy in reducing anxiety (Banks et al., [2015](#); Brown et al., [2016](#)), it is nearly impossible to conduct double-blind placebo-controlled tests of this surgical intervention. Cingulotomy reminds us of the limits of cognitive neuroscience approaches to mental disorders: Although current neuroimaging tools allow us to pinpoint malfunctioning brain regions, direct intervention in the brain itself is not always an advisable or feasible treatment option.

Verbalization and Worry

Anxious apprehension, or worry, is typically a verbal process. (This makes it difficult to study in animal models!) Uncontrollable thoughts run through the worrier's head, and these thoughts are more likely to take the form of words than images (Behar et al., [2005](#)). Therefore, it makes sense that the left frontal region, which generates speech, would be implicated. Several EEG studies have indeed found patterns of activity favoring the left frontal region among people prone to worry (Sharp et al., [2015](#)).

At first blush, these findings might seem inconsistent with the approach-withdrawal model of frontal lobe asymmetry (see [Chapter 12](#)). Isn't activation of the left frontal lobe supposed to be associated with positive, approach-related emotions? It is difficult to conceive of worry as a positive or reward-related experience. A recent study helped to solve this dilemma by using the spatial resolution of fMRI (Engels et al., [2007](#)). In this study, different subregions of the frontal lobe were associated with positive emotionality versus worry. In particular, Broca's region in the left inferior frontal gyrus was more activated in worriers, consistent with the experience of worry as internal verbalization. At the same time, a separate left dorsolateral frontal region became more active when positive than negative words were seen, consistent with the approach-withdrawal model (see [Figure 14.16A](#)).

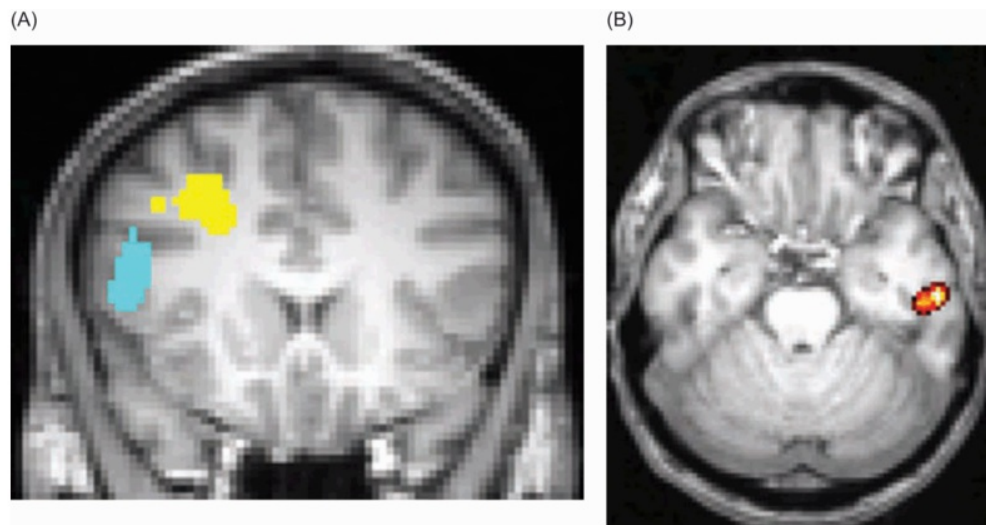


Figure 14.16 Regions associated with individual differences in anxious apprehension and anxious arousal.

(A) A region of left inferior frontal gyrus (shown in blue) was more activated in response to negative words in people who scored high on a measure of anxious apprehension, or worry, whereas regions of DLPFC (shown in yellow) were activated in response to positive words. (B) Among people who scored high on a measure of anxious arousal, or panic, a region of the right inferior temporal gyrus became especially activated by negative words.

From Figures 4 and 2 from Engels, A. S. et al. (2007). Specificity of regional brain activity in anxiety types during emotion processing. *Psychophysiology*, 44, 352–363. By permission of John Wiley & Sons, Inc.

Posterior Regions and Anxious Arousal

Whereas worry is associated with left-hemisphere verbal systems, anxious arousal is more closely associated with right-hemisphere systems that govern attentional vigilance and autonomic arousal (Sharp et al., 2015). For example, during conditions intended to provoke anxious arousal, EEG activity increases in posterior regions of the right hemisphere (Heller et al., 1997). Increased EEG activity in the right posterior region is also associated with hyperarousal symptoms in patients with PTSD (Metzger et al., 2004). An fMRI study correlated anxious arousal with increased activity in the right

inferior temporal gyrus during the processing of negative information in a Stroop task (see [Figure 14.16B](#); Engels et al., [2007](#)). Together, these findings indicate that experiences of heightened anxious arousal or panic activate the posterior right hemisphere. When designing new therapeutic interventions for anxious individuals, it may be fruitful to consider the nature of the person's anxiety, because distinct brain circuits are likely to be involved in anxious states characterized by worry compared to panic (Burdwood et al., [2016](#)).

Action Systems in Obsessive-Compulsive Disorder

The brain regions that we have discussed so far – such as amygdala and prefrontal cortex – have been implicated in more than one anxiety disorder (such as phobias or posttraumatic stress disorder). In other words, these brain systems contribute to several different manifestations of anxiety, not just one diagnostic category. However, there is one additional brain system that appears to be uniquely implicated in [obsessive-compulsive disorder \(OCD\)](#). The major behavioral feature that differentiates OCD from the other anxiety disorders is the compulsive and ritualistic actions that the person performs. Therefore, researchers have examined whether alterations in the circuits that initiate and inhibit actions may be disrupted in some way in OCD (Barahona-Corrêa et al., [2015](#)).

Of particular interest are the basal ganglia, an interconnected circuit of subcortical regions that control the initiation and cessation of movement (see [Chapter 4](#)). Numerous studies have found anatomical differences between people with OCD and control participants in the caudate nucleus, a part of the basal ganglia (see [Figure 14.17](#); Friedlander and Desrocher, [2006](#)). Symptom provocation studies – in which stimuli are presented to provoke reactions in individuals with OCD – have found increased activity in the caudate and related basal ganglia regions (Chamberlain et al., [2005](#)). Finally, successful treatment for OCD, whether through drugs or psychotherapy, appears to reduce functional activity within the basal ganglia (Nakatani et al., [2003](#)).

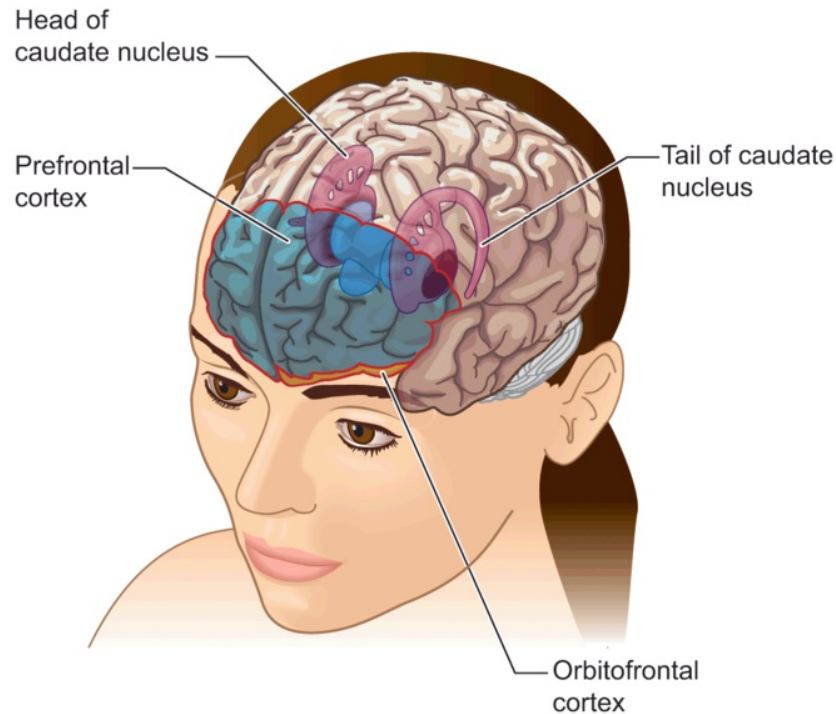


Figure 14.17 Basal ganglia are abnormal in obsessive-compulsive disorder.

Patients with OCD display anatomical abnormalities in the caudate nucleus, and functional imaging studies show increased activity in this area in response to OCD-related images. Deficits in orbitofrontal cortex have also been identified in people with OCD.

However, it is not only the basal ganglia that have been implicated in OCD; other related regions, such as the orbitofrontal cortex, also appear to show abnormalities. For example, patients with OCD are deficient in performing tasks that depend upon the orbitofrontal cortex, such as gambling tasks and tasks of reversal learning, which require responding to an item that previously was not rewarded (Cavedini et al., [2006](#); Chamberlain et al., [2005](#)).

Indeed, OCD may be best characterized by disruptions in control loops that link orbitofrontal cortex with the basal ganglia. For example, one study examined brain activity as patients with OCD were presented with stimuli (such as dirty gloves or pictures of their homes in disarray) that typically elicit their compulsive symptoms (Banca et al., [2015](#)). This symptom provocation led to simultaneous decreases in activity in the orbitofrontal region and increases in regions of the basal ganglia such as

the putamen, a pattern that was not observed in control participants. The pattern implies an imbalance in OCD between systems supporting habitual action, namely, the putamen, and those supporting goal-directed action, namely, the frontal regions.

How could disruption in an orbitofrontal–basal ganglia circuit contribute to the compulsive behaviors seen in OCD? As you remember from [Chapter 12](#), the orbitofrontal cortex plays an important role in representing the reward value of stimuli and actions. Therefore, a dysfunction in the orbitofrontal region in OCD could result in a skewed pairing of actions and rewards, such that certain actions (e.g., hand washing) become rigidly associated with reward (i.e., the reduction of anxiety). This action–reward coupling may become reinforced and difficult to overcome. As a result of the skewed reward value of the compulsive action, as well as the failure of the frontal lobes to inhibit stereotyped actions generated by the basal ganglia, the compulsive actions are repeated again and again. These aspects of OCD share some features in common with addiction, to which we turn next.

Substance Abuse and Addiction

In addition to schizophrenia, depression, and anxiety disorders, substance abuse is one of the most common mental afflictions. In any 12-month period, about 5–10% of Americans are grappling with substance use disorders, and the number increases to between 15% and 30%, depending on the survey, when lifetime prevalence is estimated (Kandel et al., [2013](#)). Substance use disorders are more common among men than women, and can occur together with other psychological problems, such as depression and PTSD (Kandel et al., [2013](#)).

Needless to say, it is difficult to draw clear lines between “use” and “abuse” of substances such as alcohol, tobacco, and illicit drugs like cocaine and heroin. Drinking a glass of wine with dinner every night does not constitute a substance use disorder, but drinking to excess in ways that threaten the safety of oneself or others is generally considered to be a problem.

The major defining feature of substance use disorders is that the person is unable to control the drug-seeking behavior even when the consequences are (or may be) severe. Severe consequences could include loss of a job and professional esteem, loss of relationships, financial losses, and even imprisonment. Yet, the addict has difficulty regulating behavior to avoid these losses; the desire for the drug outweighs these consequences.

The two main brain systems that have been related to drug abuse are the dopaminergic reward pathways and the orbitofrontal cortex, which together represent the values of rewards and punishments and act to govern behavior accordingly. In our discussion, we will consider research findings without regard to the substance abused (e.g., alcohol or cocaine) because many of the findings seem to hold true regardless of the specific substance.

Reward Pathways

Many drugs of abuse appear to activate, either directly or indirectly, the reward pathways that stretch from the midbrain to the nucleus accumbens in the basal forebrain (see [Chapter 12](#)). Through activation of the reward pathways, the drugs exert their reinforcing effects, motivating the person to come back for more. Evidence implicates the nucleus accumbens in particular. For example, lesioning the nucleus accumbens or blocking dopamine's action within the nucleus accumbens can eliminate the rewarding effects of drugs in nonhuman animals (Wise and Gardner, [2004](#)).

The development of drug dependence is likely to involve long-term changes in neurons within the reward system in response to the ongoing presence of the drugs. These changes are often thought of as “drug-opposite” adaptations because they counter the effects of the drugs themselves. For example, the reward pathways that are stimulated by addictive drugs may be especially underactive during the withdrawal state among chronic users (Wise and Gardner, [2004](#)). Several different adaptations following chronic use have been investigated at the cellular and molecular levels, including changes in receptor concentrations, intracellular signaling pathways, and morphology of

cells (Nestler, [2009](#)). At this point it is unclear which of the many cellular changes accompanying drug use is most responsible for addiction observed at the behavioral level.

Given the role of the nucleus accumbens in responding to stimuli that are rewarding or reinforcing, you might expect that people would show elevated activity in this region when viewing pictures related to their drug of choice, particularly since such cues typically elicit a strong sense of craving. Some evidence supports this expectation; for example, one study found that smokers showed greater activity in the nucleus accumbens when viewing smoking-related pictures, compared to neutral pictures (see [Figure 14.18A](#); David et al., [2005](#); see also Chase et al., [2011](#)). Another found that people who are heavy drinkers activate this region when given a small sip of alcohol (Filbey et al., [2008](#); see [Figure 14.18B](#)). Other research has shown that exposure to cues associated with amphetamine led to increased dopamine release – measured by a decreased availability of “open” dopamine receptors – in the nucleus accumbens in human participants (Boileau et al., [2007](#)).

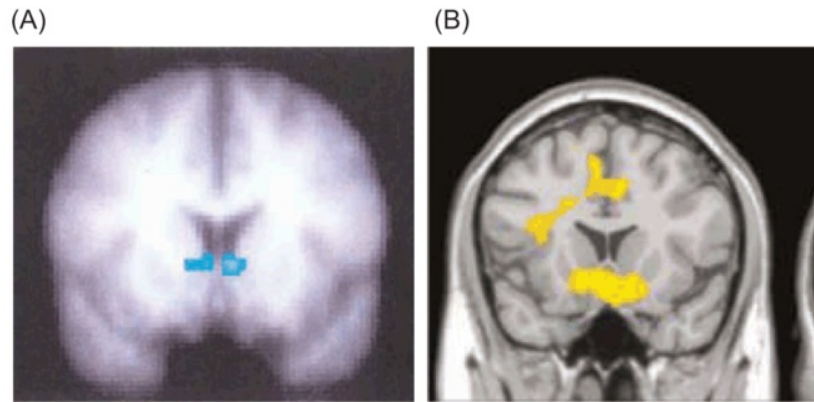


Figure 14.18 Increased activity in nucleus accumbens in addiction.

(A) When smokers viewed smoking-related pictures, compared to neutral pictures, activity was increased in the nucleus accumbens, shown here in a coronal view. (B) This same region was activated when heavy drinkers took a sip of alcohol.

Source: From Figure 2 in David, S. P. et al. (2005). Ventral Striatum/Nucleus Accumbens Activation to Smoking-Related Pictorial Cues in Smokers and Nonsmokers: A Functional Magnetic Resonance Imaging Study. *Biological Psychiatry*, 58, 488–494. With permission from Elsevier. And Adapted by permission from Macmillan Publishers, LTD: Filbey, F. M. et al. (2008). Exposure to the Taste of Alcohol Elicits Activation of the Mesocorticolimbic Neurocircuitry, *Neuropsychopharmacology*, 33, 1391–1401.

While the reward pathways are certainly critical to an understanding of addiction, several factors indicate that dopamine activity in these pathways cannot be the sole explanation for addiction. For example, while addictive stimulant drugs such as amphetamines and cocaine interact directly with dopamine neurotransmission, addictive opioid drugs such as heroin do not appear to do so (Badiani et al., 2011; Nutt et al., 2015). Therefore, a reliance on understanding dopaminergic effects in the nucleus accumbens may not fully account for all kinds of addiction. Furthermore, a number of studies have examined neural responsiveness to drug cues among chronic users and failed to find activity differences in the nucleus accumbens, although they did observe group differences in a variety of other brain regions (e.g., Schacht et al., 2013). Thus, the nucleus accumbens is not necessarily the only brain region involved in addiction. In

the [next section](#), we consider the role of another brain region that is important in substance abuse, the orbitofrontal cortex.

Orbitofrontal Cortex

The orbitofrontal cortex (OFC) is known to be important in decision making. As we learned in [Chapter 11](#) and [12](#), the OFC is important in generating expectancies about the outcomes of behavior, and these expectancies normally guide decision making. As we've seen in previous chapters, damage to this region often results in impaired decision making in real-life situations. Because drug addicts appear to have made poor choices in their lives, the OFC is a logical place to expect dysfunctions among those with substance abuse problems (for reviews, see Goldstein and Volkow, [2011](#); Lucantonio et al., [2012](#)).

Studies of the behavior of addicted people confirm that they do not weigh costs and rewards normally when making decisions. For example, while all people tend to discount large future rewards in favor of immediate but smaller payoffs, heroin addicts were even more likely than controls to undervalue long-term gains (Kirby et al., [1999](#)). Interestingly, pathological gamblers showed the same effect, demonstrating a cognitive profile similar to that seen in those addicted to drugs (Petry, [2001](#)). Another study found that, like patients with damage to the ventral frontal region, some substance abusers failed to show elevated skin-conductance responses when considering risky options in a gambling task, and they also made more disadvantageous choices than did controls (see [Figure 14.19](#); Bechara and Damasio, [2002](#)). Such performance deficits may stem from a difficulty in learning from past losses or mistakes.

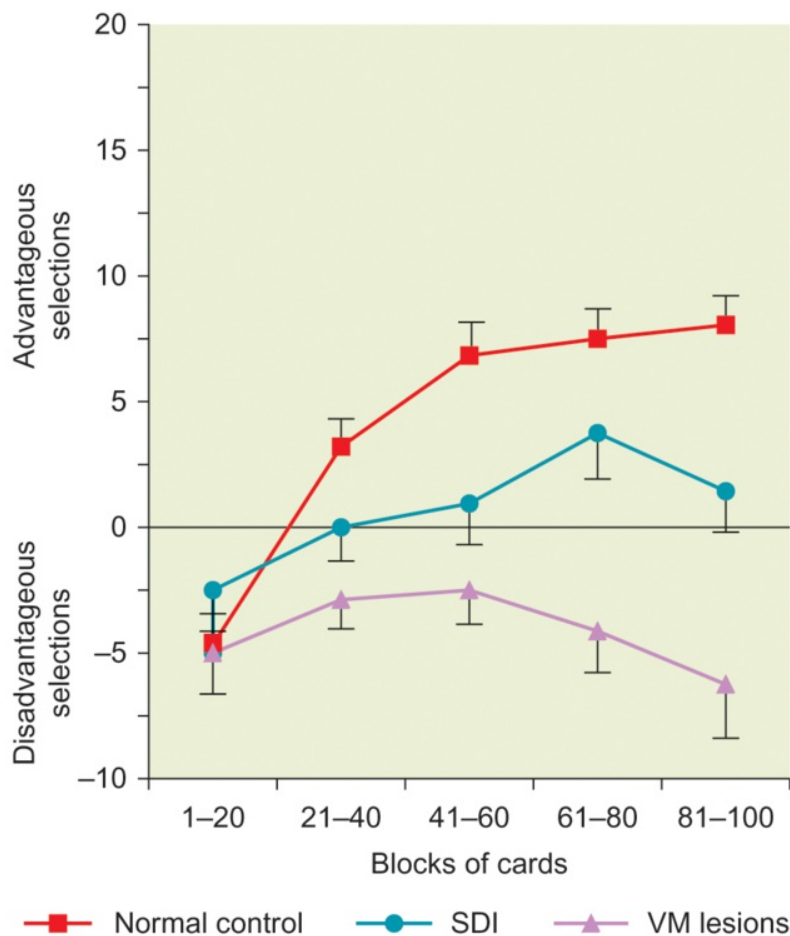


Figure 14.19 Performance on a gambling task in substance abusers, patients with ventromedial frontal damage, and control participants.

In this task, participants had to learn over time which of four decks of cards was most advantageous to select. Normal control participants show a pattern of increased selection from advantageous decks (those that return greater monetary reward). Participants with damage to the ventromedial prefrontal cortex (VM lesions) continue to choose from disadvantageous decks. Substance-dependent individuals (SDI) perform more poorly than controls but not as poorly as VM-lesioned patients.

Source: Figure 1 in Bechara, A., and Damasio, H. (2002). Decision-making and addiction (Part 1): Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia*, 40, 1675–1689. Reprinted by permission of Elsevier.

Neuroimaging evidence also indicates that the OFC region is dysfunctional in addicts. Anatomical studies show that chronic substance users have reduced gray matter

in the OFC region (e.g., Ersche et al., [2011](#)), as do those who had been drug abusers but are now abstinent (Tanabe et al., [2009](#)). At the same time, exposure to drugs or drug-related cues results in increased activity in the OFC among users, and the amount of OFC activation is positively correlated with drug craving (e.g., Brody et al., [2002](#); Dalglish et al., [2001](#)). Other research suggests that OFC may be hyperactive during acute withdrawal and underactive during more protracted withdrawal (Lucantonio et al., [2012](#)). Together with the decision-making deficits, these imaging findings make a compelling case that normal OFC function is disrupted in addicts.

But do these findings tell us that using addictive substances causes changes in OFC function, or do they tell us that people with OFC dysfunction are predisposed to become addicts? Studies of the brains of addicted people are inherently correlational; we cannot ask randomly selected people to take addictive drugs for a while and see how it may affect their brains. Therefore, the cause-and-effect relationship between substance use and OFC function is uncertain based on human studies alone. Experimental studies with nonhuman animals can offer more clues.

Some studies have found that ingestion of addictive substances can change the functioning of the OFC. For example, rats that received chronic doses of the drug amphetamine showed decreased density of dendritic spines in the OFC, in addition to increased density in the nucleus accumbens ([Figure 14.20](#); Crombag et al., [2005](#)). Chronic cocaine administration also leads both rats and monkeys to perform more poorly on behavioral tasks of OFC function, such as reversal learning (Lucantonio et al., [2012](#)). You can imagine a vicious cycle: ingesting addictive drugs disrupts the proper functioning of the OFC, and disruption of the OFC in turn leads to poor regard for the consequences of one's actions, influencing future decisions to continue drug use.

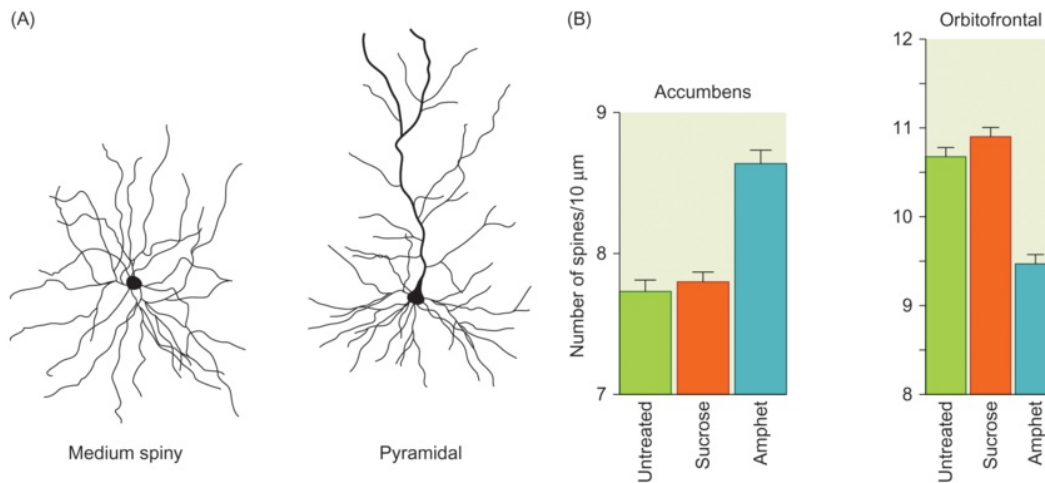


Figure 14.20 Changes in dendritic spine density following chronic exposure to amphetamines.

Researchers quantified the dendritic spines of medium spiny neurons from the nucleus accumbens and pyramidal neurons from the orbitofrontal cortex, as shown in A. Part B demonstrates that rats who were given amphetamine for 14–20 days (blue bars) showed an increase in spine density in the nucleus accumbens and a decrease in spine density in the orbitofrontal cortex, compared to sucrose-treated (orange bars) or untreated controls (green bars).

Source: Figures 1, 3, and 4 from Crombag, H. S. et al. (2005). Opposite effects of amphetamine self-administration experience on dendritic spines in the medial and orbital prefrontal cortex, *Cerebral Cortex*, 15, 341–348. Reprinted by permission of Oxford University Press.

Other research in animal models suggests that neurons in the OFC play a critical role in a phenomenon known as “context-induced relapse.” It’s long been known that addicts who are attempting to abstain are at greatest risk of relapsing into substance use when they are in a context that is associated with prior use. For example, a person may have achieved an acceptable level of abstinence while in a residential rehab program, but he or she may return to substance use when back home, in the social and physical setting in which the substance abuse had taken place. Associative cues priming the rewarding property of the drug may be especially powerful in such settings. Recent work found that neurons within the OFC were activated when rats were placed back in

a context previously associated with heroin use, and that deactivating those neurons prevented the rats from relapsing into addictive behavior (Bossert et al., [2011](#)).

Other “vicious cycle” factors may also make it difficult to break out of a pattern of drug addiction. The substance of abuse may “hijack” the brain’s frontal and limbic reward systems by lessening the reward value of other (nondrug) stimuli. In one study, cocaine addicts and nonaddicts viewed films showing scenes of people smoking crack cocaine, sexually explicit scenes, or nature scenes (Garavan et al., [2000](#)). Not surprisingly, the nonaddicts showed greatest activity in prefrontal and limbic regions in response to the sexually explicit video. These same regions were activated for cocaine addicts when viewing people smoking crack cocaine, suggesting that substances of abuse activate the same brain regions that are relevant for biological rewards. Most notably, for cocaine addicts these brain regions responded more to the cocaine video than to the sexually explicit video.

Relatedly, users of cocaine are less responsive to “social gaze,” or eye contact with others, and OFC activity in these participants was reduced, compared to controls, during a social interaction (Preller et al., [2014](#)). This pattern could make it doubly difficult to kick the habit, due to the diminished reward value of less-destructive social activities that could provide an alternative to the substance of abuse. Ultimately, a better understanding of the way various rewards are registered by the brains of people with substance use may help to improve treatment strategies.

Other Brain Regions Implicated in Addiction

Although the vast majority of studies on addiction have focused either on the reward pathways or on the orbitofrontal cortex, other regions have been implicated as well. For example, neuroimaging studies comparing activation in response to drug cues between drug users and control participants have reported group differences in various emotion-related regions such as the amygdala and insula, as well as regions implicated in

cognitive control, such as anterior cingulate cortex and dorsolateral frontal cortex (Goldstein and Volkow, [2011](#); Noël et al., [2013](#); Volkow and Morales, [2015](#)).

Among these regions, the insula has recently received special attention for its possible role in addiction (Droutman et al., [2015](#)). As you remember from [Chapter 12](#), the insula is a cortical region tucked inside the fissure between the frontal and temporal lobes, and it is thought to encode bodily states that contribute to emotional experience. Interestingly, a fairly recent report found that smokers who suffered brain damage affecting the insula lost their addiction to cigarettes (Naqvi et al., [2007](#)). One patient in this study reported that after the brain damage, his “body forgot the urge to smoke” (Naqvi et al., [2007](#), p. 534). Because addiction is closely associated with bodily sensations – the feel of a cigarette between the lips, or the sensation of smoke in the throat – perhaps the loss of those sensations made it easier to quit.

However, the fact that addicts appear to have reduced gray matter in the insula, as well as reduced functional activity in this region during craving, makes the story about the insula more complex than the simple idea that the insula is in need of deactivation in people with addiction (Droutman et al., [2015](#)). Although the puzzle has yet to be sorted out, one possibility is that the insula’s connectivity with other brain regions, such as cingulate cortex and amygdala, is somehow altered in people with addictions. This possibility reinforces a major theme in the cognitive neuroscience of psychopathology, which is that no brain region acts alone. Pathology may ultimately be best understood in terms of disrupted relationships among interacting brain areas rather than simple underactivations or overactivations in certain areas.

Conclusions and Caveats

This chapter should convey that a great deal of research effort is being expended in trying to understand the neurocognitive correlates of mental disorders. This research is motivated both by the desire to develop treatments that will improve the lives of people suffering from these disorders, and by the desire to understand the basic science of the

brain's workings. At the same time, you have probably become aware of some of the serious limitations on our knowledge in this area. Indeed, despite the many dollars and research hours expended, attempts to understand psychopathology using neuroscience methods still fall frustratingly short at the present time.

One major obstacle to progress is the complexity of the clinical conditions themselves. Each category of disorder is characterized by heterogeneity in symptoms, making it difficult to study “pure” profiles of disorder. Comorbidity between different disorders also adds to the problem of identifying unique features of specific disorders. For example, people with PTSD are also at increased risk for substance abuse, so studies of PTSD need to take possible substance abuse into account. Further, it is often unclear whether a particular neural marker, such as activity in a certain brain region, is associated with a diagnostic category (e.g., major depressive disorder) or whether it is associated with a particular symptom (e.g., apathy) that might cut across different diagnostic categories.

For these reasons, recent research initiatives have moved away from research designs that simply compare people who fall into a particular diagnostic category with “pure” control participants who have no evidence of the disorder (Kozak and Cuthbert, [2016](#); Patrick and Hajcak, [2016](#); Sharp et al., [2015](#)). The traditional approach, which has been widely used in many of the studies reviewed in this chapter, assumes that mental illness is a categorical phenomenon (you either have it or you don't), when in fact most problems likely exist along a continuum.

In addition, a simple “comparing groups” approach assumes that everyone within a category, such as those with a major depressive disorder, is more or less alike, when in reality they may share some symptoms and not others, and they may differ in the severity of their symptoms, even if they all received the same diagnosis. A more productive approach may be to examine not diagnostic categories, but rather more specific psychological constructs that are tied to pathology, such as threat responsiveness,

arousal, or reward motivation, and to understand what causal factors affect the entire range of individual differences in those processes.

You may also have noticed that many of the same brain regions are implicated in different disorders reviewed in this chapter. For example, the prefrontal cortex, the amygdala, the cingulate cortex, and the reward systems are each implicated in more than one disorder. There is no one-to-one correspondence between a dysfunctional brain region and an observable mental disorder. Ultimately, researchers want to know more about how a particular regional dysfunction contributes to a characteristic of a specific disorder. For example, we need to know not only that prefrontal function is disrupted in both schizophrenia and depression, but also how information is processed by that brain region, in interaction with other regions, in a way that manifests itself as a feature of schizophrenia in one case but depression in another case. The problems are extremely complex, but the motivation to solve them is strong and is likely to remain so.

Summary

Schizophrenia

- Symptoms of schizophrenia generally fall into two categories: negative and positive symptoms. Negative symptoms include flat affect and catatonia. Positive symptoms include delusions, hallucinations, and disorganized thought.
- Frontal lobe functions such as working memory, planning, and voluntary control of eye movements are deficient in schizophrenia. A common neuroimaging finding is hypofrontality, or reduced frontal activation.
- Temporal lobe regions are also dysfunctional in schizophrenia, particularly in the left-hemisphere regions implicated in auditory comprehension and speech perception.
- Disruptions in coordinated activity among brain regions may also contribute to disorganized thought and hallucinations in schizophrenia.

Depression

- Depression is defined by a loss of ability to feel pleasure, combined with feelings of helplessness, hopelessness, and disruptions in sleep and appetite.
- People who are depressed perform poorly on frontal lobe tasks, particularly tasks that require allocation of effort or learning from feedback. Dorsolateral prefrontal cortex and regions of the anterior cingulate cortex regions have been implicated as functioning atypically in depression.
- Evidence indicates decreased activity in the left frontal region, compared to the right frontal region, in people who are depressed or at risk for depression.
- Depression is further characterized by changes in limbic system structures such as the amygdala, reward pathways, and hippocampus.
- New treatments for depression, such as rTMS, DBS, and VNS, attempt to intervene on a neurological level when mainstream treatments, such as pharmacotherapy and behavioral therapy, do not work.

Anxiety Disorders

- There are many different subtypes of anxiety disorders, including phobias, panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and generalized anxiety disorder. All involve fear reactions that are out of proportion to the circumstances.
- The amygdala plays a key role in anxiety disorders, which is not surprising given its role in fear learning and extinction. Anxiety disorders may also be characterized by poor frontal lobe regulation of subcortical structures such as the amygdala. Such dysregulation can contribute to an inability to extinguish acquired fears and an increased attentional bias toward threatening cues.
- Two dimensions of anxiety, anxious apprehension and anxious arousal, have been linked to different neural correlates. Anxious apprehension, or worry, is

associated with activity in the left frontal region near speech areas. Anxious arousal is associated with elevations in right-hemisphere systems of arousal and attentional vigilance.

- The basal ganglia motor structures are involved in the compulsive and ritualistic actions observed in obsessive-compulsive disorder.
- Individual differences in anxiety and depression are linked to variations in the serotonin transporter gene, which influences neurotransmission in the serotonin system. Individuals who have an “S” gene variant respond more strongly to negative information than do those with two copies of the “L” gene variant.

Substance Abuse and Addiction

- The main feature of substance abuse is the inability to stop drug-seeking behavior even when the consequences are very bad.
- Studies in nonhuman animals indicate that the reward pathway, from the midbrain to the nucleus accumbens, plays an important role in the reinforcing effects of many addictive drugs and the neural adaptations that occur with chronic substance use.
- Accumulating evidence indicates that orbitofrontal cortex function, particularly the ability to weigh positive and negative outcomes, is disrupted in substance abusers. Other regions, such as the insula, amygdala, and cingulate cortex, have also been implicated in addiction, but their specific role is not yet certain.

Chapter 15

Brain Development and Plasticity



Development of the Brain

Changes in the Brain During Childhood

Synapse Formation and Pruning

Myelination

Changes in Functional Connectivity

Associating Neural and Cognitive Development

Changes in the Brain During Adolescence

Influence of the Environment on the Developing Brain

Environmental Enrichment and Deprivation

Sensitive Periods in Development

Developmental Disorders

Intellectual Disability

Genetic Disorders

Infections and Toxins

Dyslexia

Autism

Attention-Deficit/Hyperactivity Disorder

Brain Plasticity in Adulthood

Recovery of Function Following Brain Damage

Neurophysiological Responses to Insult

[Regional Mechanisms for Recovery of Function](#)

[Recovery of Function in Adults](#)

[Recovery of Function in Children](#)

[In Focus: Can Deprivation in One Sensory Modality Promote Extraordinary Abilities in Another?](#)

[Changes in the Brain With Aging](#)

[Cognitive Changes With Aging](#)

[Neural Changes With Aging](#)

[Slowing the Effects of Aging](#)

[Summary](#)

To all who knew him, Dan appeared to be a relatively intelligent 12-year-old with a friendly and cooperative manner. Yet, he was struggling in his schoolwork, especially in spelling and reading. These troubles were nothing new. Despite considerable remedial training, these subjects had always been difficult for him. When a school counselor suggested neuropsychological assessment, his parents agreed willingly, hoping that it might shed some light on his problems.

Neuropsychological testing revealed no evidence of gross brain damage. His sensory, perceptual, and motor abilities all appeared normal and his overall IQ was in the average range. A more detailed analysis of his abilities revealed that his visuospatial skills were quite good. His score on the Visual Spatial Index of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V), which emphasizes visuomotor and visuospatial abilities, was above average, and he performed well on a number of other tests assessing nonverbal problem solving. In contrast, his performance on the Verbal Comprehension Index of the WISC-V was below average. A number of additional verbal tests revealed that he had little appreciation for the phonemic structure of words. He read words by guessing what they were on the basis of their salient visual features or

configuration, rather than by trying to sound them out. For example, he read form as “farm,” theory as “those,” grieve as “great,” and tranquility as “train track.” He exhibited similar problems in the spelling of orally presented words, spelling square as “s-c-a-r,” cross as “c-o-r-s,” and triangle as “t-r-e-r-e.”

Given that his difficulties were long-standing and that remediation so far had not been effective, the neuropsychologist diagnosed Dan as having a specific verbal learning disability that is commonly known as dyslexia. She suggested that further intervention for reading be geared to capitalize on Dan’s good visuospatial abilities, such as teaching him to carefully distinguish words on the basis of their visual features and using flash cards to drill him on the form of words. An incremental approach could be taken; he could first acquire knowledge about simple words and then apply it toward reading more complicated material. For example, once Dan could learn to recognize fly, he could then use that knowledge to help read other words, such as butterfly.

The neuropsychologist also explained to Dan’s parents that even with such remediation, he would probably never become a highly fluent reader, which meant that some aspects of formal schooling would remain challenging. However, she also emphasized that such difficulties did not preclude future occupational success for Dan. In fact, numerous famous people are known to be dyslexic, including the actor Tom Cruise, the artist Pablo Picasso, and Ann Bancroft, the first woman to cross the ice to both the North and South Poles. The neuropsychologist suggested to Dan’s parents that they encourage him to pursue areas of study and interests that would capitalize on his above-average visuospatial abilities.

The case study in the opening vignette of this chapter illustrates some of the important ways in which neuropsychological disorders observed developmentally can differ from those observed later in life. In adults, the inability to read is often associated

with damage to particular regions of the left hemisphere (see [Chapter 8](#)). However, in Dan's case, no evidence of localized brain damage was apparent. Whereas adults with alexia have acquired the ability to read and then lost it, Dan never acquired the ability to read with a reasonable degree of proficiency. Thus, cognitive deficits can have different origins and different neural correlates, depending on whether they were acquired in adulthood or during the process of development.

The case of Dan and children with other developmental disorders helps us to realize that the brain is dynamically changing: that is, the brain exhibits [plasticity](#). A child's brain is not the same as an adult's brain, and yet in both children and adults the brain is exquisitely sensitive to environmental input. In this chapter, we examine how the brain develops and the ways in which it remains plastic or malleable across the lifespan. First we review the major processes of developmental change in the brain in childhood and adolescence. We also consider developmental disorders, such as dyslexia and autism, from a cognitive neuroscience perspective. We then discuss how the adult brain can adapt to changing experience. Finally, we consider how the brain responds to damage or insult, and conclude with an examination of the changes in cognitive and neural processes associated with aging.

Development of the Brain

The brain changes in numerous ways from the beginning of life to adulthood. As you can imagine, an infant's brain does not look exactly like an adult's brain! You might think that the brain simply grows bigger as the child grows bigger, but the story is actually quite a bit more complex. While some aspects of neural development can be thought of simply as "growth" or proliferation, other aspects involve a more complex sculpting of nerve cells, their pattern of connections, and their organization. At all stages of development, from childhood through adolescence and adulthood, the challenge for researchers is not only to document how the brain changes, but also to understand how physical changes in the brain relate to developing cognitive and emotional skills.

Changes in the Brain During Childhood

[Figure 15.1](#) gives an overview of the time course of major events during neural development. You can immediately notice several things from this figure. First, many processes take place during development, including cell proliferation and migration, development of synapses, and myelination. Second, each of these processes has its own time course; some processes take place primarily before birth, whereas others continue throughout adolescence. Finally, development cannot be thought of simply as a linear progression of growth. As you can see from the figure, processes such as the generation of synapses show an inverted-U function, rising and then falling, indicating initial increases and proliferation followed by subsequent reduction, pruning, or sculpting.

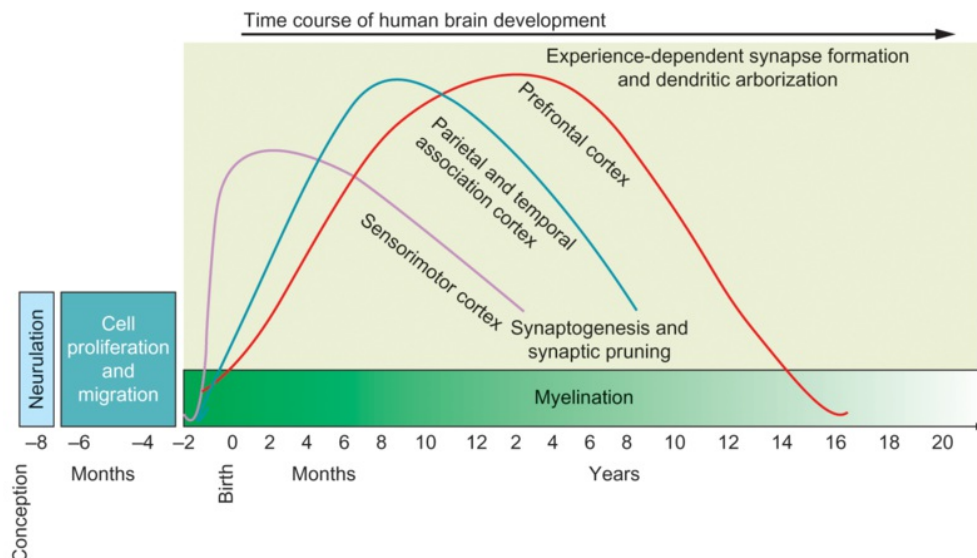


Figure 15.1 Overview of the time frame of human brain development.

Shown here is the time course of different processes involved in brain development, from conception through young adulthood.

Source: Figure 1 from Casey, B. J. et al. (2005). Imaging the developing brain: What have we learned about cognitive development? Trends in Cognitive Sciences, 9, 104–110. Reprinted by permission of Elsevier.

To understand brain development, let us start at the beginning (for review, see Silbereis et al., 2016). Early in fetal development, after the simple primordial fertilized

egg differentiates into specific types of tissue (e.g., muscle, skeletal, cardiovascular, nerve), the spinal cord and brain are nothing more than a hollow tube. The formation of this tube is referred to as [neurulation](#). With time, the tube folds, twists, turns, and expands to become the fetal brain, while the hole inside the tube becomes the ventricular system.

Around the seventh week of gestation, the nerve cells and glia near the inside of the tube divide, proliferate, and then begin to migrate outward. [Neurogenesis](#), or the generation of new nerve cells, occurs in the area right around the ventricle (see [Figure 15.2](#)). In this process, the tube acts much like a port around which the initial neural settlers will reside. As more neurons are generated, the central areas around the ventricle become settled, and then the new neurons, like new immigrants to a city, must traverse further out to find a place to live. As the brain grows, new neurons travel further and further out to the metaphorical suburbs of the brain. Glial cells provide the scaffolding or “roads” along which nerve cells can migrate to their ultimate destinations ([Figure 15.3](#)). Thus, the six layers of cortex are built from the inside out; the first set of cells migrates to the deepest (innermost) layer of the cortex (the sixth), the next set of cells to the fifth cortical layer, and so forth.

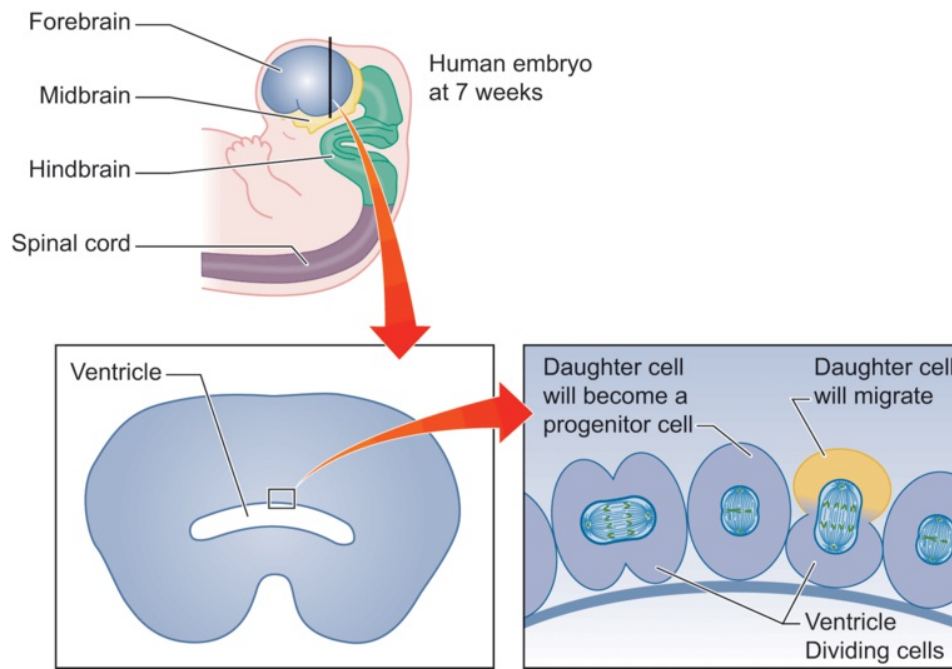


Figure 15.2 Neurogenesis.

The creation of new nerve cells in embryonic development occurs in the ventricular zone. Progenitor cells that line the ventricles can divide, producing new daughter cells. The daughter cells can either stay in the ventricular zone and act as new progenitor cells, or they can migrate away from this zone and into other areas of the brain.

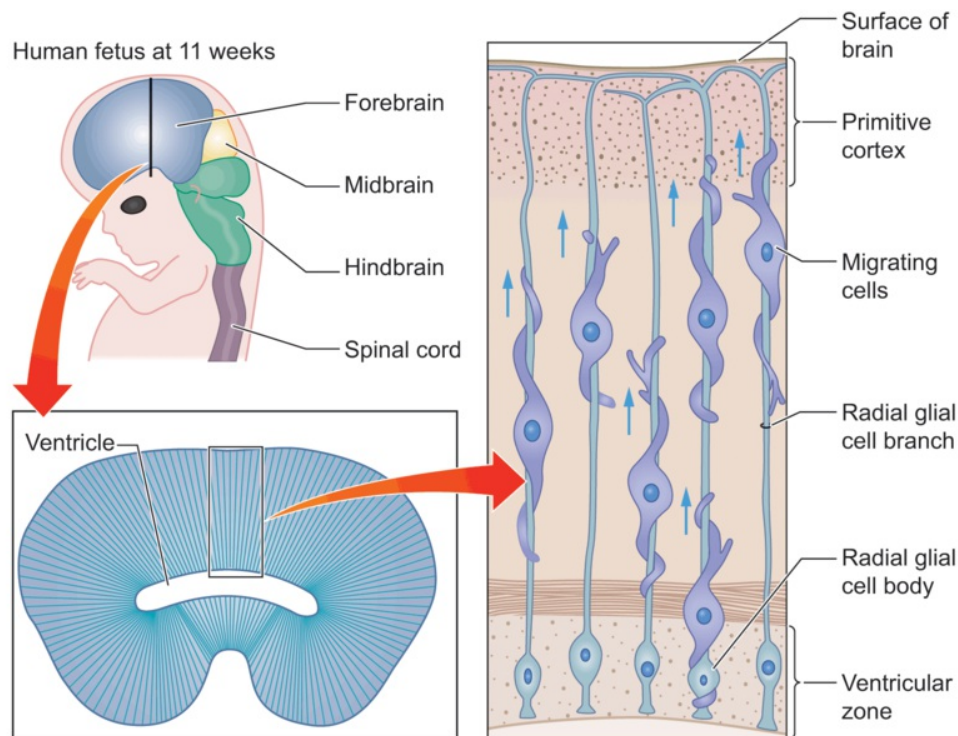


Figure 15.3 Migration of nerve cells.

Cells that migrate away from the ventricular zone often travel along radial glia, which form a kind of scaffolding along which the cells can migrate.

By six months of gestation, most neurons have been produced. Because the development of the cortex is protracted during gestation, there is ample opportunity for disruption of the typical pattern. We will discuss syndromes involving disrupted development later in this chapter, including dyslexia and fetal alcohol syndrome.

Synapse Formation and Pruning

One of the largest changes after birth is a dramatic increase in the number of connections (synapses) that neurons make with other neurons. This process is known as [synaptogenesis](#). As illustrated in [Figure 15.4](#), dendrites in cortical regions increase greatly in number early in life, providing greater surface area for synaptic connections. Synaptogenesis occurs so rapidly that the total number of synapses increases more than tenfold within the first year of life! Based on the number of synapses ultimately formed and the typical time frame of synaptogenesis, researchers estimate that synapses form at

a staggering rate of 4.3 million per minute during peak periods of synaptogenesis (Silbereis et al., [2016](#)). The dramatic increase in synapses, combined with the subsequent paring down of those synapses, is one of the most important mechanisms of plasticity in the developing brain.

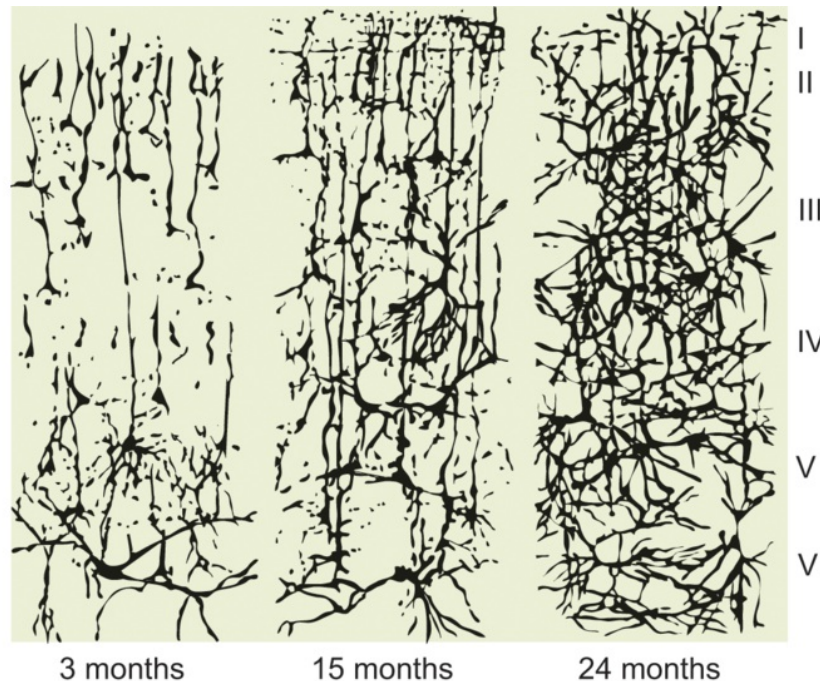


Figure 15.4 Increases in dendrites during early development.

Shown here are representative sections of the brain of (a) a 3-month-old child, (b) a 15-month-old child, and (c) a 24-month-old child. The numerals to the right of (c) indicate the six layers of cortex.

The process of synaptogenesis does not occur equally across all regions of the human brain at the same point in development. Rather, there are regional differences (Huttenlocher, [2002](#); see [Figure 15.1](#)). Synaptogenesis occurs most rapidly in the primary sensory and motor areas first, followed by association areas and prefrontal cortex. This makes sense from a functional point of view; a baby needs to get basic sensory and motor skills up and running before more complex abilities can come on-line.

An important feature of synapse formation is its inverted-U function over time, often described as a “blooming and pruning” pattern (see [Figure 15.1](#)). After synapse

proliferation (“blooming”), pruning occurs through the elimination of synapses, which reduces the number of connections between neurons. Just like synaptic blooming, the pruning of synaptic connections occurs at a staggering rate. For example, researchers estimate that as many as 60 axons per second in the corpus callosum are lost during the first few weeks of a monkey’s life, and in humans the loss may be even greater – as many as 200 axons per second (LaMantia and Rakic, [1990](#); Rakic, [1991](#)). This pruning happens in part because cells that do not receive so-called “survival factor” signals from their neighboring cells undergo apoptosis, or programmed cell death. In other cases, the cells themselves do not die, but their synapses are disassembled and their axons retract or degenerate (Low and Cheng, [2006](#)).

Like synaptogenesis itself, the time course of synaptic elimination varies among cortical regions. For example, histological studies indicate that pruning is complete in the human visual cortex by 10 years of age, but continues in the frontal cortex until adolescence and beyond, into the third decade of life (Huttenlocher, [1979](#); Petanjek et al., [2011](#)). Structural MRI studies have confirmed that changes in cortical thickness occur at different points during development depending on the brain region (Gogtay et al., [2004](#); Toga et al., [2006](#)). Nevertheless, across cortical regions, by adulthood the number of synapses is about 40% less than the peak value during childhood (Huttenlocher and de Courten, [1987](#)).

What is the functional purpose of a developmental pattern of synaptic blooming and pruning? One possibility is that synaptic overproduction allows the brain initially to have maximal capacity to respond to the environment. Then, during development, the neurons or connections that do not receive much stimulation wither away. This enables the brain to fine-tune and specialize for its specific environment (Bourgeois, [2001](#); Huttenlocher, [2002](#)). Interestingly, a longitudinal MRI study found that children with higher intelligence, measured by a standard IQ test, tend to show a greater rate of cortical thickening early in development, as well as a greater rate of cortical thinning later in development, particularly in frontal lobe regions (Shaw, Greenstein et al.,

[2006](#)). Assuming that cortical thickness is due in part to the number of synapses, these data suggest that superior intelligence may be correlated with faster rates of change in both the synaptic proliferation and pruning processes, a trend that continues into adulthood (Schnack et al., [2015](#)).

The importance of synaptic blooming and pruning is also illustrated by developmental disorders in which these events go awry. For example, the brains of people who have disorders associated with mental retardation show reductions in the complexity of the dendritic trees, the length of dendrites, or both. Furthermore, the spines on their dendrites tend to have atypical form, such as being longer and thinner than usual (Kaufmann and Moser, [2000](#)). Other disorders, such as fragile X (which we discuss later in this chapter), are associated with an elevated density of spines along dendrites, suggesting a failure of synapse elimination (Grossman et al., [2006](#)).

Myelination

As you know, nerve cells are not the only cells in the brain; glial cells also play an important role in brain structure and function. We have already learned that certain types of glial cells form scaffolding during development that helps nerve cells find their way to distant destinations in the brain. Another very important role of glial cells is to provide the myelin sheath that coats axons in the brain. A baby's brain is relatively unmyelinated, which means that it lacks the oligodendrocytes that insulate neurons. Therefore, brain regions cannot interact quickly in the infant.

Myelination is a long, drawn-out process, with a developmental course that varies widely by region of the nervous system (Simmonds et al., [2014](#)). Myelination first begins to appear between the fourth gestational month and the first year after birth (see [Figure 15.5](#)). Not surprisingly, the brain regions that are myelinated earliest in life, such as the spinal cord and the medulla, are those that support basic functions. During the first year after birth, basic sensory and motor systems become myelinated. Later in childhood, myelination occurs for connections between integrative systems, such as those connecting cortical and subcortical areas and those linking different cortical

regions. For example, myelination of the corpus callosum continues through the teens into the early twenties (e.g., Lenroot et al., [2007](#); Thompson et al., [2000](#)) as do long-range connections between different regions of the brain. The net result of all this myelination is that the relative amount of white matter increases during childhood and the teenage years while the amount of gray matter decreases (see [Figure 15.6](#)) (Brain Development Cooperative Group, [2012](#); Giedd et al., [2015](#)).

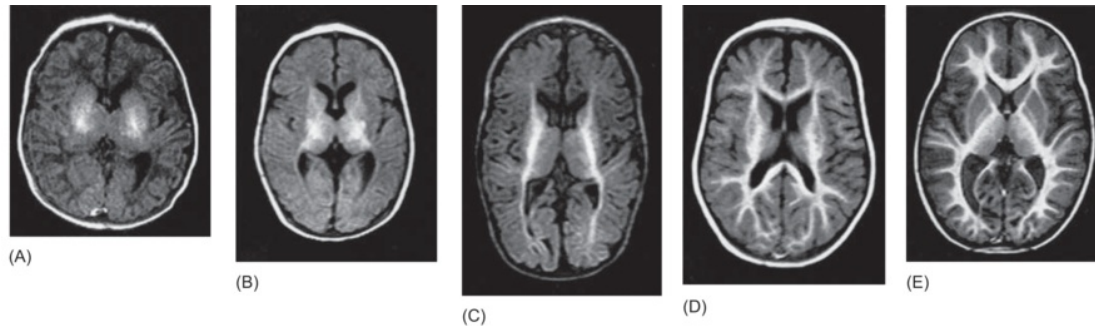


Figure 15.5 Increased myelination of the brain during infancy.

In these figures, myelin appears in white. (A) 1-month-old infant; (B) at 2 months; (C) 3–6 months; (D) 7–9 months; (E) older than 9 months.

(from Knapp and Valk, [1990](#))

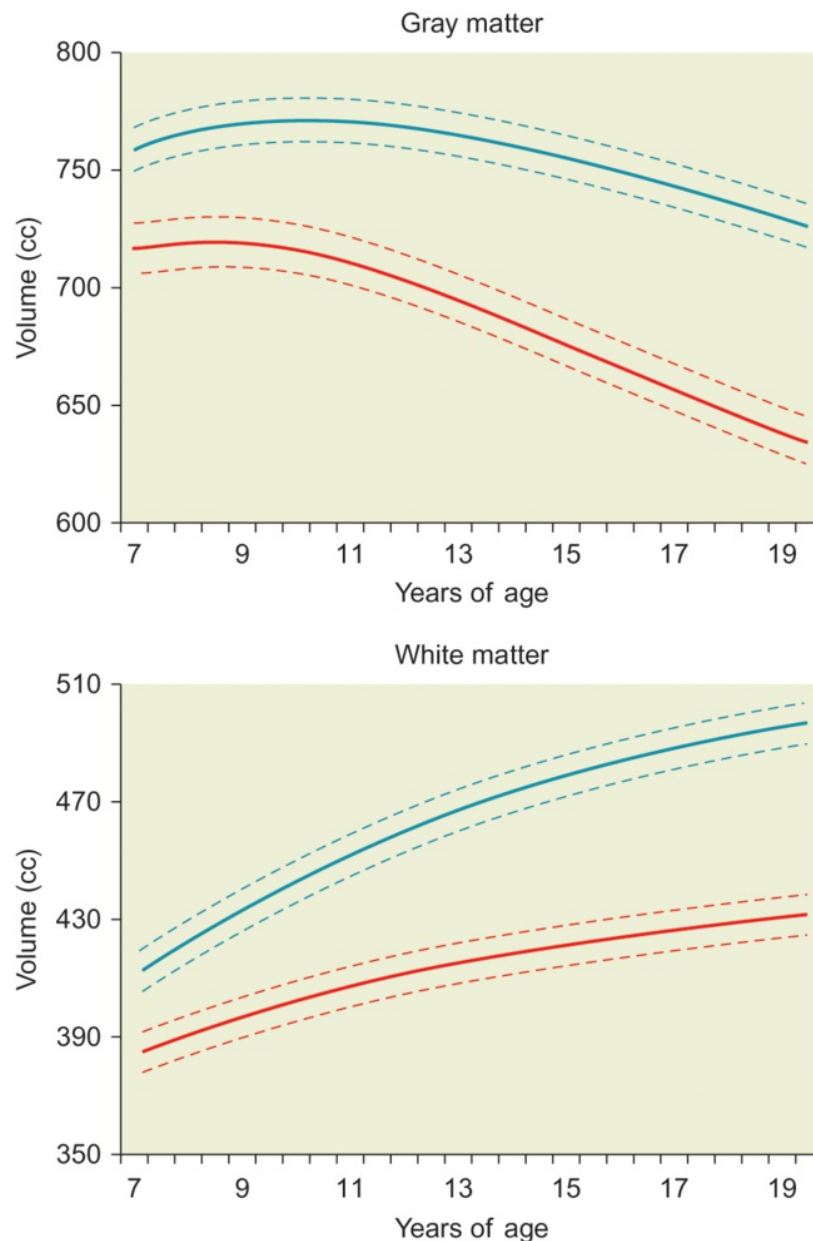


Figure 15.6 Between middle childhood and adulthood, gray-matter volume generally declines due to synaptic pruning, while white-matter volume increases due to myelination.

The figure also illustrates that brain volume is generally larger in boys (blue line) than in girls (red line) for both gray and white matter.

(from Lenroot et al., [2007](#))

The consequence of myelination is that brain regions become more structurally interconnected during development, up through adulthood (Dennis et al., [2013](#)). This, in

turn, results in increased communication between brain regions. It is as if the baby's brain were connected by a series of old country roads meandering from town to town. This system doesn't make for fast travel. Myelin transforms this infantile system into a faster one – the old country roads become regional highways, and even more myelin transforms them into national superhighways that can handle large volumes of traffic moving quickly. Faster transmission of neural signals can support quicker and more integrated perception, cognition, and action.

Changes in Functional Connectivity

Given that myelination continues throughout childhood and adolescence, providing an enhanced structural framework for communication between brain regions, we should expect that coordinated activity between brain regions also changes during this period. Here, the emphasis is not just on developmental changes within localized brain regions, but rather on how networks of interacting brain regions may coordinate their activities differently as development unfolds.

Indeed, studies of functional connectivity have documented developmental changes in interregional coordination (Grayson and Fair, [2017](#)). For example, one fMRI study, focused on functional connectivity of the anterior cingulate cortex, found that adults showed more long-distance functional co-activations, whereas children showed more local functional co-activations (Kelly et al., [2009](#)). Using EEG methods, researchers have also found that patterns of synchronized activity across the brain become more ordered (less random) with development during the childhood years (Smit et al., [2012](#)).

Based on patterns of functional connectivity, it is even possible to predict the age of the person whose brain is being imaged. In one study, more than 200 people between the ages of 7 and 30 were scanned during a resting baseline condition for a mere five minutes (Dosenbach et al., [2010](#)). Researchers used a multivariate pattern analysis approach to quantify patterns of brain activity across widespread cortical networks, including 160 distinct cortical regions. Based on the patterns of functional connectivity,

a computer program was able to categorize the brain as either a child or adult with 91% accuracy. (You may wonder about those adult brains that were mistakenly categorized as children – perhaps they are similar to your grown-up uncle who still seems like a boy. And the children’s brains that were miscategorized as adults – perhaps they are child prodigies. The study did not address these questions.)

Although it may seem like there are easier ways to tell if someone is a child or adult – and indeed there are! – such studies are intriguing in their use of brain imaging data to draw conclusions about characteristics of specific individuals. More generally, the study supports the conclusion that functional connections within networks of brain regions, just like aspects of brain anatomy, show developmental changes between childhood and adulthood.

Associating Neural and Cognitive Development

Needless to say, all these changes in brain physiology – changes in synaptic density, myelination, and functional connectivity – are mirrored by changes in the cognitive and behavioral repertoire of the child. Children in all cultures tend to acquire both cognitive and motoric skills in an orderly fashion: Babbling precedes speaking, and crawling precedes walking. Furthermore, specific abilities are acquired within specific age ranges. For example, in preschool years, children are able to engage in imaginary play and they begin to develop theory of mind, the ability to cognitively represent the mental states of others. In literate societies, children begin learning to read generally between the ages of 5 and 7 years. Because such changes typically occur in an orderly fashion and at a particular age, they are known as [developmental milestones](#).

Major behavioral changes during early development are listed in [Table 15.1](#). The table also lists the average size of the brain at each developmental stage, to give you a sense of the brain’s overall growth. Of course, as you know from the preceding sections, it is not simply the growing size of the brain that supports different cognitive abilities.

Rather, the complex pattern of interconnections among brain areas, sculpted by maturation and experience, is what drives behavioral and cognitive development.

Table 15.1 Development Changes During Early Childhood

| AGE | Visual and Motor Function | Social and Intellectual Function | Average Brain Weight (g) |
|------------|--|--|---------------------------------|
| Birth | Exhibits sucking, rooting, swallowing, and Moro reflexes; engages in infantile grasping; blinks to light | – | 350 |
| 6 weeks | Extends and turns neck when prone; regards mother's face; follows objects with eyes | Smiles when played with | 410 |
| 3 months | Exhibits infantile grasping and sucking modified by volition; keeps head above horizontal for long periods; turns to objects presented in visual field; may respond to sound | Watches own hands | 515 |
| 6 months | Grasps objects with both hands; will place weight on forearms or hands when prone; rolls supine to prone; supports almost all weight on legs for brief periods; sits briefly | Laughs aloud and shows pleasure; emits primitive articulated sounds, "gagoo"; smiles at self in mirror | 660 |
| 9 months | Sits well and pulls self to sitting position; uses thumb-forefinger grasp; crawls | Waves bye-bye; plays pat-a-cake; uses "dada," "baba"; imitates sounds | 750 |

| | | | |
|-----------|---|--|-------|
| 12 months | Is able to release objects; cruises and walks with one hand held; exhibits plantar reflex (50% of children) | Says two to four words with meaning; understands several proper nouns; may kiss on request | 925 |
| 24 months | Walks up and down stairs (using two feet per step); bends over and picks up objects without falling; turns knob; can partially dress self; exhibits plantar reflex (100% of children) | Uses two- to three-word sentences; uses "I," "me," and "you" correctly; plays simple games; points to four to five body parts; obeys simple commands | 1,065 |
| 36 months | Goes up stairs (using one foot per step); pedals tricycle; dresses and undresses fully except for shoelaces, belt, and buttons; visual acuity 20/20 | Asks numerous questions; knows nursery rhymes; copies circle; plays with others | 1,140 |

Although development undoubtedly entails changes in brain functioning as well as changes in behavior, finding a direct causal link between a change in a specific aspect of neural functioning and the emergence of a certain cognitive function has proven surprisingly difficult. Currently, there are relatively few cases in which we can point to a biological marker that predicts development of a specific cognitive process. Furthermore, even when we do find such a marker, the connection between the physiological process and the cognitive function is unclear.

To illustrate the challenges in associating a developmental change in cognition with a developmental change in the brain, consider a specific study of white-matter development associated with reading competence (Myers et al., [2014](#)). Researchers measured white-matter development longitudinally in children when they were 5–6 years old, and then again when they were 8–9 years old. Increases in white matter in

regions of the left hemisphere, including the arcuate fasciculus, predicted the extent of improvements in reading ability over the three years of the study (see [Figure 15.7](#)).

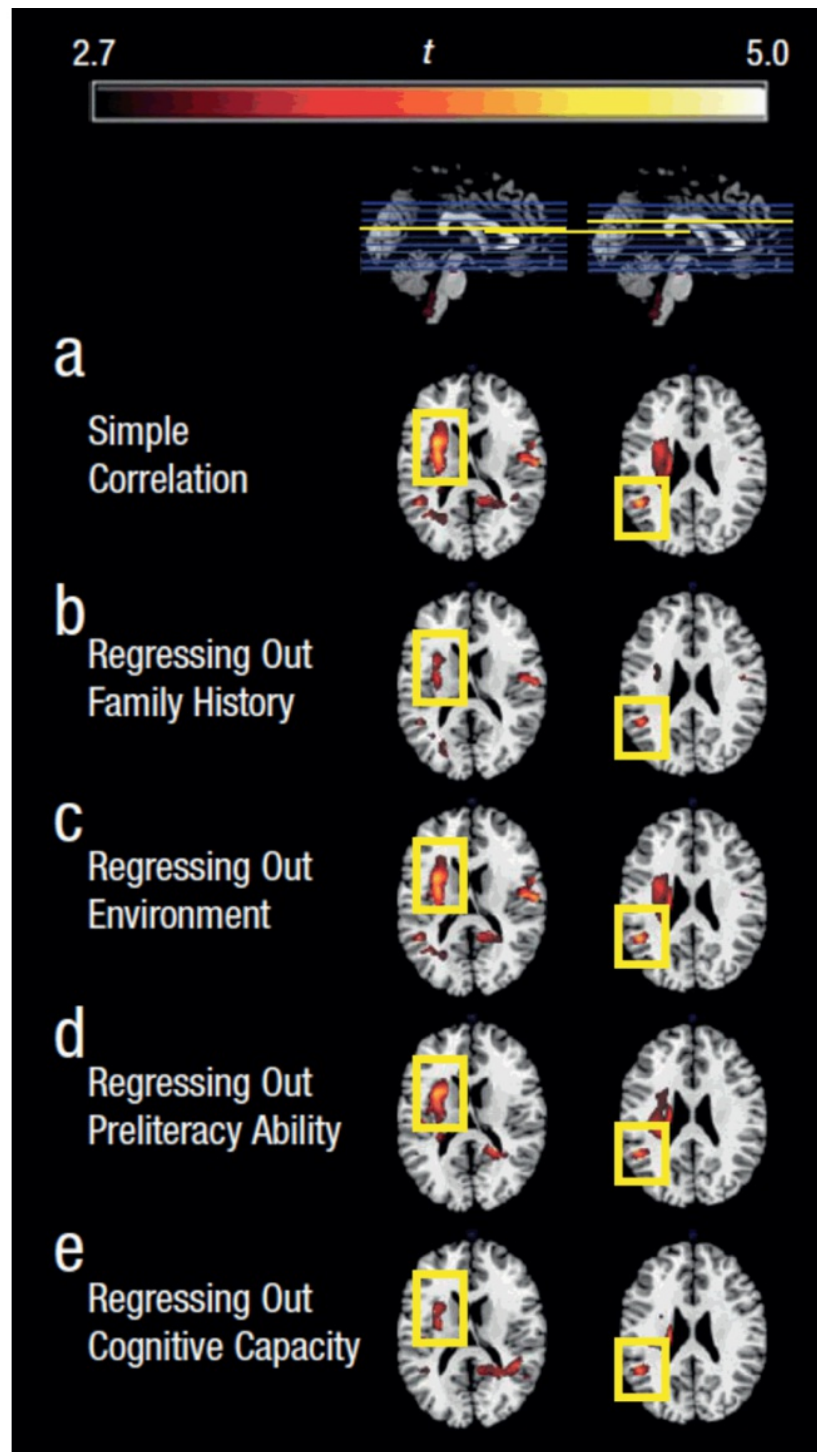


Figure 15.7 Regions in which increases in white matter during early childhood predict improvements in reading competence.

In a longitudinal study, researchers examined correlations between increases in white matter and increases in reading competence between ages 5 and 8, a period when most children learn to read. Row (a) illustrates the regions in which correlations between white matter and reading development were significant, and rows (b) through (e) illustrate the regions in which the correlations between white-matter and reading remained significant even once researchers statistically controlled (regressed out) other possible contributing factors such as family history of reading disability, socioeconomic status (“environment”), the child’s pre-literacy skills such as rhyming ability and spoken vocabulary, and the child’s overall cognitive level. These results point to the importance of white matter development in contributing to the development of a specific aspect of cognition, in this case reading.

(from Myers et al., [2014](#))

Importantly, these correlations between increasing white-matter development and increasing reading skill held true even when researchers statistically controlled for a number of factors including the socioeconomic status of the child’s family, the parents’ own history of reading difficulties (if any), and the child’s pre-literacy skills (such as vocabulary and the ability to parse the sounds of language). Thus, it appears that the association between white matter and reading ability cannot be accounted for by these other potential factors.

However, finding a robust association, as is the case here, does not disambiguate whether the development of white matter in these regions causes the improvement in reading, or whether enhanced cognitive skill in reading stimulates the development of the white matter. This is because, in general, correlational studies have difficulty identifying which causal pathway accounts for relationships between aspects of neural and cognitive development. Although a deeper understanding of the causal mechanisms of developmental change is elusive, researchers often assume that a particular neurobiological substrate must be in place before specific cognitive and emotional

abilities can manifest themselves, much the way that particular motor aspects of the nervous system must be developed before a child can walk.

Changes in the Brain During Adolescence

Although much research on brain development has focused on the early childhood years, recent studies have also focused on understanding the transition from childhood to adulthood. This transitional period is generally known as adolescence, and roughly covers ages 12 to 20, or the time when people are in secondary rather than primary (elementary) school. We've already seen that some aspects of brain development continue through adolescence and beyond. For example, changes in myelination and synaptic pruning occur well into the teen years and onward into the twenties.

Research on the adolescent brain has tended to focus on neural changes that can be related to the prominent cognitive and emotional characteristics of teenagers. For example, although adolescents are cognitively sophisticated, they tend to make riskier choices than adults (as you can probably confirm based on episodes from your own life!). In addition, social competency is especially important in adolescence, as navigating the complexities of peer groups becomes crucial. Finally, adolescence is a time of emotional turmoil. Therefore, maturation of brain areas that govern complex decision making, social cognition, and emotion regulation may have special implications for the development of the adolescent mind.

Can neuroscience explain why teenagers tend to drive too fast, fail to wear seat belts, and engage in risky substance use? One prominent model, known as the dual-systems model, argues these behaviors can be understood as a result of a developmental "mismatch" between two systems. One system, the prefrontal cognitive control system that exerts top-down control over lower brain regions, is still developing at this time of life. However, the lack of prefrontal maturation cannot be the whole story. The prefrontal cortex is more mature in adolescents than in younger children, and yet it is the adolescents, not the younger children, who typically display riskier behavior. To understand this pattern, we must consider another system, the limbic reward regions

such as the nucleus accumbens. As limbic structures mature in adolescence, they create more powerful incentives to seek exciting rewards. So it is the mismatch between these highly active limbic structures and the still immature prefrontal cortex that leads to risky behaviors. Such behaviors are thought to decrease in adulthood because as prefrontal regions mature, they can exert better and better control over limbic regions (Casey et al., [2008](#); Steinberg, [2008](#); Shulman et al., [2016](#)).

Consistent with this model, multiple studies have found that activity in the nucleus accumbens and other ventral striatal structures is increased in adolescents both when they anticipate and when they receive a reward. This activity level in the ventral striatum is higher in adolescents compared to younger children, and also higher compared to adults. And in longitudinal studies, activity in the striatum peaks in mid-adolescence and then declines thereafter. At the same time, activity in the lateral region of the prefrontal cortex is lower in adolescents compared to adults (see Shulman et al., [2016](#), for review). Putting these two pieces together, the adolescents displayed a unique pattern, not seen in either children or adults, of elevated limbic responses in combination with relatively lower prefrontal responses. The exaggerated limbic response to rewards could explain why when no reward is involved, adolescents tend to show adult-like skills in logical reasoning. However, when strong emotional incentives are present, they are much more likely to make risky choices (see also Somerville et al., [2011](#); Steinberg, [2005](#)).

Researchers are also especially interested in the adolescent brain because many forms of psychological distress either emerge for the first time or become worse during the adolescent years. For example, during adolescence, the risk for depression increases to adult levels for the first time, and the gender difference in depression emerges (e.g., Davey et al., [2008](#); Hyde et al., [2008](#)). Substance abuse and schizophrenia may also have their first onset during the adolescent years. Of course, there are numerous social as well as biological reasons why psychological disorders may increase in this time period, as people's bodies and their social standing can both change dramatically, eliciting strong emotional reactions. We know from previous chapters that top-down

control by the prefrontal regions over limbic regions is important in regulating emotions. During adolescence, the connection between these regions is still tenuous and social-emotional challenges are great. Therefore, it should not be surprising that difficulties in regulation of emotion may manifest during these years. In the long run, understanding the unique features of the adolescent brain may help explain why certain social-emotional problems emerge during this time period (Luciana, [2013](#)).

While controlling emotional impulses is an important key to surviving adolescence, understanding the complex social world is also crucial (Blakemore, [2010](#); Somerville, [2013](#)). Adolescents tend to be obsessed with social status and belonging to social groups. This, in turn, requires a level of cognitive sophistication in order to understand what other people think and feel. For example, adolescents are quicker than younger children in answering questions about another person's perspective (e.g., "A girl is not allowed to go to her best friend's party. How does she feel?"; Choudhury et al., [2006](#)). As discussed in [Chapter 13](#), certain brain regions – such as the medial prefrontal region, temporoparietal junction, and superior temporal sulcus – are believed to be important in understanding the thoughts and feelings of others. These regions are activated in both adolescents and adults during tasks that require making inferences about another person's mental state (compared to tasks that require inferences about physical causality); however, the pattern of activation is slightly different, with adolescents showing stronger activity in the medial prefrontal region and adults showing stronger activity in the superior temporal sulcus (Blakemore et al., [2007](#)). These findings imply that adults and adolescents may be using different strategies to draw conclusions about other people's mental states.

In sum, adolescence is a distinct developmental state, not simply an intermediate waystation between childhood and the beginning of adulthood. Unique neurobiological and psychological characteristics differentiate adolescence from childhood and adulthood. Understanding the specific cognitive, emotional, and neural features of adolescence is important not only for scientific reasons, but for the implications for

public policy (e.g., Steinberg, [2013](#)). For example, in [Chapter 17](#), we consider how scientific understanding of the adolescent brain may alter conceptions of how juveniles should be treated in the criminal justice system.

Influence of the Environment on the Developing Brain

The child's brain does not develop in a vacuum. Rather, it develops in a dynamic world full of sights, sounds, smells, tastes, and tactile sensations. As the child grows, he or she is not only receiving sensory experiences from the world, but is also actively exploring the world. How does the child's experience within the world influence the developing brain? What kinds of experiences are necessary for normal brain development, and what kinds of experiences can modulate the basic pattern of brain development? Does it matter when certain experiences occur in a child's life?

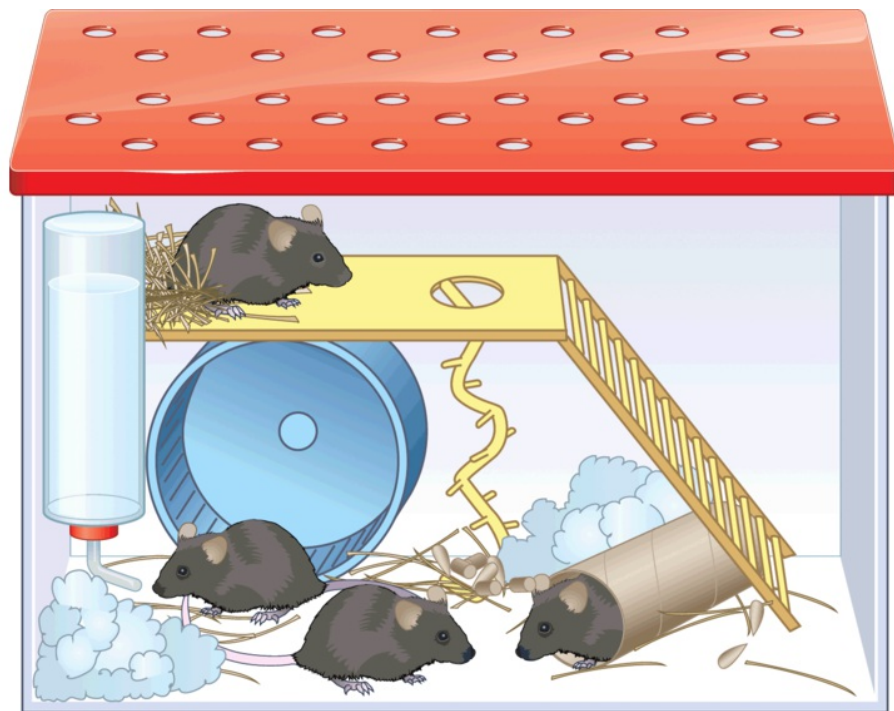
Researchers have distinguished between two broad categories of experience that can influence the developing nervous system (e.g., Bruer and Greenough, [2001](#)). First, some kinds of experiences are common to nearly all members of the species. Any newborn human is virtually guaranteed to be exposed to patterned light, to social interactions, and to some kind of language; only in extreme cases are people deprived of these experiences. Therefore, evolution could count on these experiences to be present during development, and information from these sources, though essential for normal development, did not have to be specified in the genetic blueprint. Instead, the nervous system evolved to "expect" these kinds of experiences from the environment. The neural systems that respond to such experiences are known as [experience-expectant systems](#); they develop normally when the expected input is received, but are seriously affected when the expected experience is absent. For example, in extremely rare cases in which an individual is exposed to no language, the development of the language system is grossly abnormal (Curtiss, [1977](#)). Likewise, complete social deprivation produces abnormal social behavior (Harlow et al., [1965](#)). Within the visual system, the normal

development of binocular depth perception depends on having normal exposure to light in both eyes during development (Horton and Hocking, [1997](#); Wiesel and Hubel, [1963](#)).

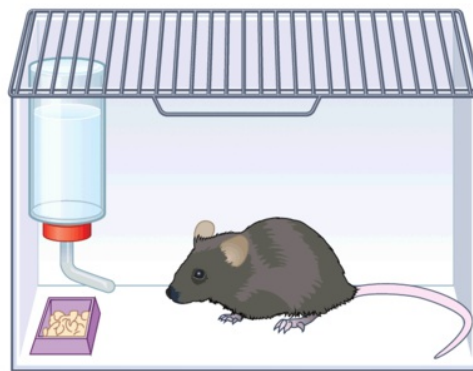
Experience-dependent systems, in contrast to experience-expectant systems, are those that vary across individuals and are based on their personal, unique experiences. For example, some children are exposed to musical training early in life, while other children are placed into pee-wee hockey clubs. These children are likely to develop different levels of musical and motor control skills. The nervous system does not require these specific experiences to develop normally; for example, a person without formal musical training still has a normal nervous system, unlike a child who is deprived of language input throughout childhood. Thus, whereas experience-expectant systems are considered species-typical (developing in all people except in extreme circumstances), experience-dependent systems differ more widely across people as a result of different life circumstances.

Environmental Enrichment and Deprivation

Perhaps not surprisingly, enriched environments are generally better for cognitive and brain development than impoverished ones. Decades of research with rodents have found that an enriched or stimulating environment can affect the structure of neurons, causing the dendrites of the neurons to become bushier and the number of synapses per neuron to increase (e.g., Rosenzweig et al., [1972](#); Turner and Greenough, [1985](#); see Sale et al., [2009](#), for review). An enriched environment for a laboratory rat typically consists of a spatially complex living area combined with social stimulation (see [Figure 15.8A](#)). In contrast, the control (impoverished) environment consists of a small standard-issue clear plastic cage where the animal lives alone (see [Figure 15.8B](#)). Enriched environments can influence synaptic connectivity not only during early development but also in adulthood, and changes persist to some degree even when the animals are later removed from the enriched setting (e.g., Briones et al., [2004](#)).



(A)



(B)

Figure 15.8 Enriched versus impoverished environments for rats.

(A) In the complex environment condition, the animals are allowed to spend hours each day in an environment characterized by a large area in which the spatial arrangement of items and toys is changed daily (for variety) and in which the rats have the opportunity to interact with other rats. (B) In contrast, in the control condition the rat remains alone in a small plastic cage all day.

Neural changes following environmental enrichment may provide for more and varied connections, increasing the brain's computational power so that it can effectively deal with a more cognitively demanding and complicated environment. Animals raised in complex environments are superior to control animals in aspects of perceptual

sensitivity and in solving various maze-learning tasks (e.g., Bourgeon et al., [2004](#); Leggio et al., [2005](#); Williams et al., [2001](#)). Interestingly, female rats reared in enriched environments tend to transfer their superior maze performance to their pups (Friske and Gammie, [2005](#))! Although it is not clear exactly how the benefits of environmental enrichment are transferred from mothers to pups, one possibility is that mothers raised in enriched environments bestow a more beneficial kind of maternal care upon their pups, which then enhances or aids the pups' ability to learn.

Most studies of environmental enrichment have been conducted in other species, in which researchers can experimentally manipulate rearing conditions. In studies of people, it can be harder to conduct true experiments such that certain aspects of the rearing environment are manipulated while controlling for all other relevant variables. As a result, some human studies rely on correlational evidence to suggest that particular experiences may shape brain development. For example, one study found increased white matter in the corpus callosum among young adults who began musical instruction before the age of 7 years, compared to nonmusicians or those who began musical training when they were older than 7 (Steele et al., [2013](#)). While the results hint that musical training can impact white-matter development, the study cannot definitively prove a cause-and-effect relationship because participants were not randomly assigned to musical training groups. For example, children who started music lessons at an earlier age may have grown up in a more enriched environment than those who started later, who may not have had access to music lessons earlier. In other words, other environmental variables could potentially account for the relationship observed between callosal connectivity and musical training.

Other studies attempt to experimentally manipulate children's experiences, and therefore their brain development, through specific training programs. In one study, researchers trained 5-year-old children in certain aspects of attention (Rueda et al., [2012](#)). In one training exercise, intended to work on inhibitory control, children had to help a cartoon farmer bring sheep into a fenced area by clicking on sheep as quickly as possible, but withholding responses when the animal turned out to be a wolf instead of a

sheep. Other training exercises developed skills of resolving discrepancies between conflicting information and remembering perceptual information. After 10 sessions of training, trained children (compared to untrained children) demonstrated ERP responses during a conflict resolution task that looked more like those of an adult. Furthermore, EEG data suggested more focused activity in regions of the executive attention network in the trained children, compared to broader, more diffuse patterns of activation in those who did not receive training. These results give some clues about how very specific learning experiences may affect development of executive functions (see also Diamond and Lee, [2011](#)).

Such training studies focus on manipulation of certain aspects of a child's experience, but these manipulations represent only a tiny fraction of the varying experiences of different children in the real world. Taking a different approach to understanding the role of environmental factors on brain development, other researchers have compared children from economically impoverished versus well-off circumstances. These studies have the advantage of addressing real-life discrepancies in children's experience, but they also have the disadvantage that such experiences cannot be experimentally controlled or manipulated. In general, studies have found that children raised in less-than-ideal conditions, as indexed by lower socioeconomic status, show poorer cognitive performance than children raised in households with higher socioeconomic status (e.g., Farah et al., [2006](#); Noble, [2014](#)). We return to this area of research in [Chapter 17](#), where we consider implications of neuroscience research for issues of pressing concern to society.

Rarely can researchers experimentally manipulate the entire environment of a child. But one exception is the remarkable work of a project referred to as the Bucharest Early Intervention Project (Nelson et al., [2014](#)). At the time of the study, the standard of care for orphaned or abandoned children in Romania was to be placed in a state-run orphanage, where the chances for social interaction and intellectual stimulation were quite poor. The research team was able to establish a comprehensive training program for at least some of these deprived children to be placed with foster families. Children

were randomly chosen to remain in the orphanage or to be placed with a highly trained foster family. The results were clear: children who were reared in the foster families scored better on nearly every measure of development than those who remained institutionalized, including IQ, language development, white-matter development, and organized patterns of neural oscillatory activity measured by EEG ([Figure 15.9](#); Bick et al., [2015](#); Fox et al., [2011](#); Nelson et al., [2007](#); Vanderwert et al., [2016](#)). These results attest to the pervasive sensitivity of brain development to the surrounding environmental circumstances.

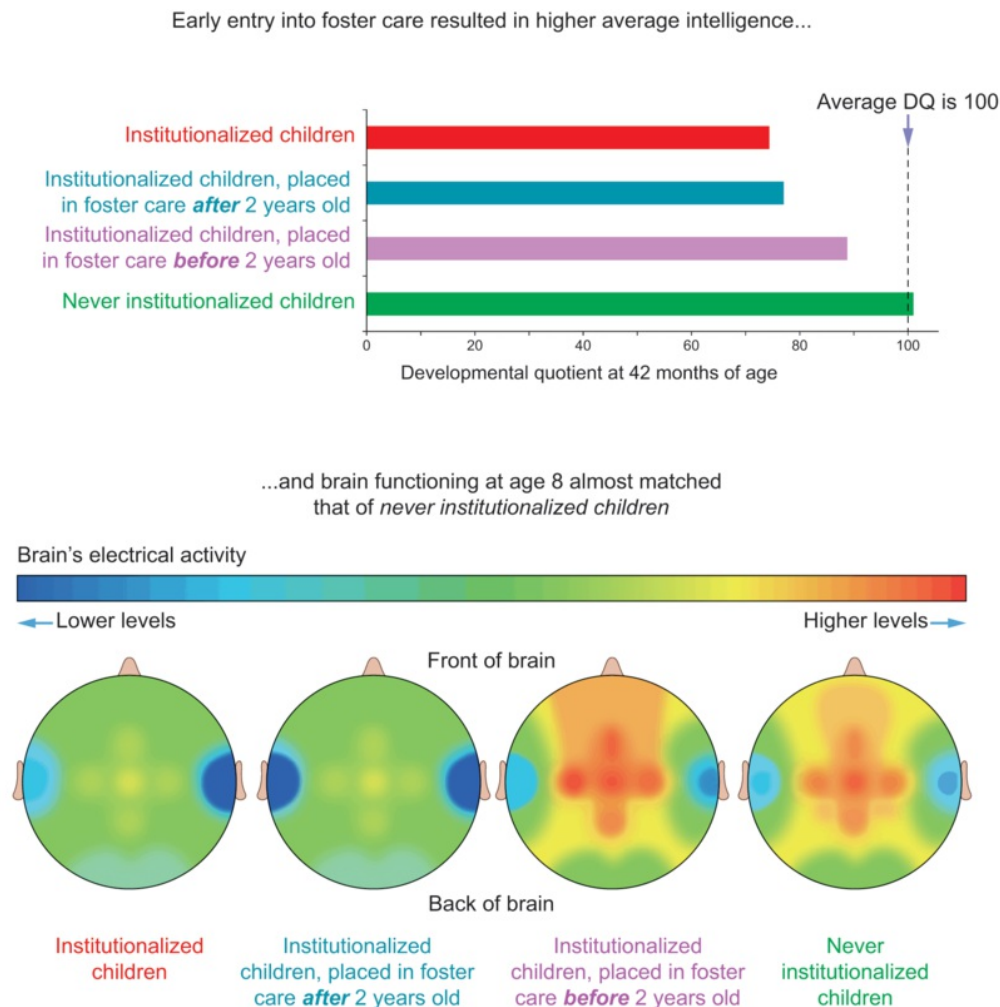


Figure 15.9 Effects of environmental deprivation during critical developmental windows in orphaned Romanian children.

Children were assigned to either continued orphanage care or placement with a foster family. Upon follow-up, those assigned to foster families showed improvements in IQ (top panel) and patterns of EEG activity that more closely resembled children raised in normal family settings. However, the benefits only accrued to children who were placed in family homes before two years of age, demonstrating the need for family care during critical early years of development.

(from Nelson et al., [2013](#))

Sensitive Periods in Development

The impact of an environmental experience upon the brain and cognitive development may depend on the timing of its input. Although certain environmental effects can

influence the organism across a lifetime, in other cases the organism is particularly sensitive to certain external stimuli during a specific developmental period, known as a [sensitive period](#). Such time periods allow the brain to incorporate information from the environment and then to “lock in” that information.

Some examples of sensitive periods in development come from the visual system. For example, some children are born with cataracts, which make the lens of the eye opaque and therefore prevent light from entering the eye. Research has shown that it is crucial to have such cataracts removed immediately in order for vision to develop normally. Even a few months of early visual deprivation due to cataracts can disrupt the ability to develop normal face-perception skills (Maurer and Lewis, [2013](#)). Having cataracts that develop after about age 7 to 9 is not as detrimental to visual acuity as having cataracts before that age, indicating that normal visual input for the first seven years of life is important in developing adult levels of acuity.

Research in other species also demonstrates that visual deprivation in early life has significant consequences for visual function. For example, suturing one eye shut during early development in cats or monkeys affects the responses of cells in the primary visual cortex (Horton and Hocking, [1997](#); Wiesel and Hubel, [1963](#)). Research using animal models has identified particular molecular signals that influence the “opening and closing” of the sensitive period for visual development, including neurotrophins that promote plasticity in the developing visual cortex and glycoproteins that inhibit axonal growth and therefore reduce plasticity in the adult visual cortex (Berardi et al., [2003](#); Trachtenberg, [2015](#)).

Deprivation of social contact during sensitive periods also affects neural and cognitive development. For example, one study found that socially isolating mice for a period of two weeks following weaning led to alterations in myelination and prefrontal cortex development (Makinodan et al., [2012](#)). The isolated mice were unable to recover normal structure and function even when placed back in social environments. In humans, true social isolation is extremely rare, but studies of children raised in orphanage

settings suggest that social deprivation in childhood is associated with alterations in white matter (Sheridan et al., [2012](#)). Furthermore, the typical N170 ERP response to faces (see [Chapter 6](#)) is blunted in children who spent their early years in an orphanage, compared to noninstitutionalized children of the same age (Parker and Nelson, [2005](#); Parker et al., [2007](#)). Children raised in institutional settings past the age of 2 appear to show more severe deficits in structure and function than those placed in family homes before the age of 2, implying a window of time in which species-typical social rearing is most critical (see [Figure 15.9](#); e.g., Nelson et al., [2007](#)).

The development of language also involves a period of maximal sensitivity to input, demonstrating that higher cognitive functions also depend upon input at particular time periods (Friedmann and Rusou, [2015](#); Kuhl, [2010](#)). For example, evidence from second-language acquisition supports the notion of a sensitive period for language development. If acquisition of a second language occurs before the ages of 5 to 7 years, the person's competence will be equivalent to that of a native speaker (see [Figure 15.10](#)). For each year that passes after the age of 7 without exposure to the language, there is an incremental decline in the ability to understand the grammatical constructions of that language (Johnson and Newport, [1989](#); see also Gleitman and Newport, [2002](#); Newport et al., [2001](#)). This pattern of results suggests that the ability to acquire a high degree of grammatical competence in a second language is limited by biological factors (see also Huang et al., [2014](#)).

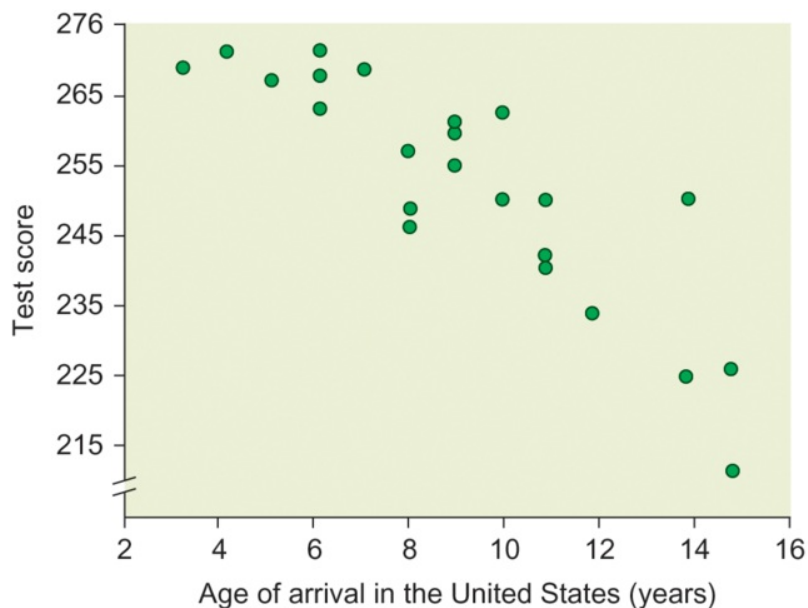


Figure 15.10 Sensitive period for acquiring grammatical competence in a second language.

The relationship between age of arrival in the United States and grammatical competence for individuals who arrive while between ages 3 and 15 years. With each year that passes after the age of five years, the ability to acquire grammatical competence decreases.

What specific biological mechanisms control the timing of the sensitive period for language acquisition? Currently the answer to this question is not known. Models of vocal communication in other species may provide some clues in the future. For example, many songbirds must be exposed to songs of their species within a critical window of development in order to learn those songs, and researchers have begun to identify neural processes that also change around the time that the critical period for song learning closes (Brainard and Doupe, [2013](#); Mooney, [2009](#)). In humans, one model holds that the sensitive period for language learning opens due to the brain's overall increasing computational power combined with the emergence of specific systems for social cognition that enable learning from others (Kuhl, [2010](#)). The mechanisms for the closing of the sensitive period – that is, the biological factors that make it more difficult for adults to learn language compared to children – are still yet to be discovered.

In sum, the development of the brain and behavior involves marvelously complex processes that unfold over a period of more than 20 years. Developmental processes in the brain include cell proliferation and migration, synaptogenesis, synaptic pruning, myelination, and alterations in functional connectivity, all of which take place over different time frames and at somewhat different rates in various brain regions. Some processes, such as cell migration, appear to progress relatively independently of environmental input. Others, such as synaptogenesis, synaptic pruning, and myelination, appear to be exquisitely sensitive to both the presence of species-typical environments (experience-expectant effects) and the presence of specific and unique environments that the child encounters (experience-dependent effects). Unfolding maturational processes combine with both universal and unique experiences at certain periods of development to produce a cognitively developed adult.

Developmental Disorders

Conditions such as intellectual disability (mental retardation), dyslexia, autism, and attention-deficit disorder are known as developmental disorders because they typically make their first appearances during childhood, and because they represent a departure from the normal developmental path. Much is still unknown about the original causes of these conditions and how they unfold during development. Here we consider current understanding of several major classes of developmental disorders.

Intellectual Disability

When children fail to acquire intellectual abilities across most cognitive domains at a normal rate and manner, and when they have difficulties in adaptive functioning such as self-care, the disorder is termed intellectual disability, also referred to as mental retardation. Intellectual disability is not associated with a particular focal lesion, but rather tends to result from factors that have a pervasive effect on many developing brain systems.

Intellectual disability is generally divided into four categories based on severity. This classification system and the characteristics of individuals in each category are presented in [Table 15.2](#). Intellectual disability can be caused by numerous factors, including genetic disorders, infections, toxins, and oxygen deprivation (e.g., Huang et al., [2016](#)). As we learned earlier in this chapter, the developing brain is plastic and can be affected by the environment to a greater degree than can the adult brain. Although one of the virtues of this plasticity is that the brain can fine-tune itself to the environment, the downside of plasticity is that the brain is also more vulnerable to negative influences.

Table 15.2 The Four Classes of Intellectual Disability Based on Severity

| Degree of Disability | IQ Level | Percentage* | Typical Presentation |
|----------------------|----------------|-------------|---|
| Mild | 50–55 to 70 | 85 | <p>Develop normally during preschool but do not acquire academic abilities above the sixth-grade level.</p> <p>As adults, can usually be self-supporting, and may live independently with community and social support.</p> |
| Moderate | 35–40 to 50–55 | 10 | <p>Can acquire communication skills during early childhood.</p> <p>As adults, need some supervision for living and work (such as group homes) but can take care of themselves in those contexts.</p> |
| Severe | 20–25 to 35–40 | 3–4 | <p>Can learn some elementary self-care and language skills.</p> <p>As adults, need supervision and</p> |

assistance for living and work, but can perform simple tasks in closely supervised settings.

| | | | |
|----------|--------|-----|--|
| Profound | <20-25 | 1-2 | Have impairments during childhood in sensorimotor functioning. Usually have an identifiable neurologic disorder that accounts for the retardation. |
| | | | Need highly structured environment with constant supervision by an individual caregiver. |

* Percentage of all intellectually disabled children who fall into that category.

Genetic Disorders

Numerous genetic disorders can cause intellectual disability (Ropers, [2008](#); Vissers et al., [2016](#)). Here we review just two of these conditions – Down syndrome and fragile X syndrome – as examples of genetic conditions that have a pervasive influence on mental development.

[Down syndrome](#) is the most common genetically caused syndrome of intellectual disability (see Wiseman et al., [2009](#), for review). It is associated with severe disability, with IQs typically in the lowest 2% of the general population. This syndrome, which occurs in about 1 in 700–800 births, is caused by trisomy 21, a condition in which the 21st pair of chromosomes contains three chromosomes (trisomy) rather than the usual two ([Figure 15.11](#)). Down syndrome is characterized by a specific morphology of the body and face ([Figure 15.12A](#)), which can aid early diagnosis. People with Down syndrome have pronounced deficits in language and verbal memory, with somewhat better functioning in visuospatial and social tasks. Several studies have described a developmental trajectory in which raw scores on various cognitive measures show improvement over childhood development; yet children with Down syndrome exhibit a

slower rate of cognitive development than their peers without the syndrome, so their IQ scores (which are based on comparisons with typically developing peers) decline over the course of development (Patterson et al., [2013](#)).

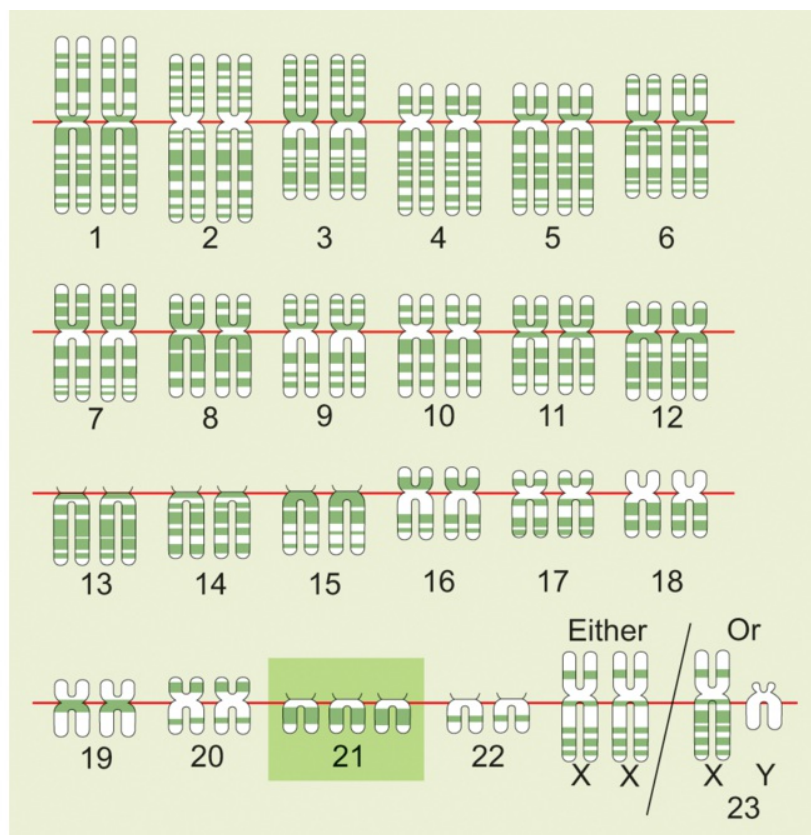


Figure 15.11 The inheritance of three copies of the 21st chromosome results in Down syndrome.



Figure 15.12 Physical features associated with genetic causes of intellectual disability.

(A) Individuals who have Down syndrome typically have certain physical features that make this type of disability relatively easy to detect in infancy. These features include an upper eyelid that, at the corner of the eye, folds over the bottom eyelid, and a face with a relatively flat profile. Source: George Doyle/JupiterImages. (B) The physical features associated with fragile X syndrome are much less pronounced. As shown here in this adolescent male who has the syndrome, they include a long face, a prominent forehead, and large ears. However, as can be seen, these features are not so out of the ordinary as to make the diagnosis obvious.

Source: Zumawirewestphotos/Newscom.

Down syndrome is characterized by reduced gray-matter volume, which is primarily attributable to reductions in cortical surface area (Adeyemi et al., [2015](#); Lee et al., [2016](#)). As they enter the fourth or fifth decade of life, many people with Down syndrome begin to exhibit symptoms similar to those of Alzheimer's disease (see [Chapter 16](#)). Postmortem examination of the brain reveals the tangles and plaques typical of Alzheimer's disease as early as the teen years in children with Down syndrome (Lemere et al., [1996](#)). This relationship between trisomy 21 and Alzheimer's-like cellular pathology may ultimately yield clues about genetic contributions to both Down syndrome and Alzheimer's (e.g., Shi et al., [2012](#)).

Another inherited form of mental retardation is [fragile X syndrome](#), which affects 1 in 7,000 boys and 1 in 11,000 girls (for review, see Hunter et al., [2014](#)). In this syndrome, an individual inherits an X chromosome with a “fragile” section. At this section of the chromosome, a normally repeating sequence of genetic material occurs an unusually large number of times, much like a genetic stutter. As a result, less than the normal amount of a protein called the Fragile X Mental Retardation Protein (FMRP) is produced. Postmortem studies show that dendritic spines appear to be overabundant and have an immature shape in people with fragile X. Research is therefore focused on understanding the role of the FMRP protein in dendritic development (e.g., He and Portera-Cailliau, [2013](#); Pfeiffer and Huber, [2009](#)).

The degree of cognitive impairment in fragile X syndrome varies, ranging from profound to borderline (Huddleston et al., [2014](#)). In contrast to Down syndrome, visuospatial impairment appears to be somewhat worse than verbal impairment among those with fragile X syndrome. Interestingly, some evidence indicates that the magnocellular pathway within the visual processing stream – the pathway especially concerned with coarse patterns and motion – is especially affected (Koukoui and Chaudhuri, [2007](#); see also Kéri and Benedek, [2011](#)). Physically, people with fragile X syndrome often have a characteristic look, although it is much more subtle than that of Down syndrome. Fragile X syndrome produces a tendency toward a long, narrow face; a long, prominent chin; and large ears ([Figure 15.12B](#)). Children with fragile X syndrome are often not diagnosed until later in childhood, when they begin to fall behind their peers in development.

Infections and Toxins

The developing fetus is exposed to many different substances that pass through the placenta, the membranous organ through which blood and nutrients are transferred from the mother to the fetus. Most of what is transferred through the placenta is beneficial and

essential for the developing fetus, but some substances can be harmful. These include infectious organisms as well as toxic substances ingested by the mother.

Infections that can potentially damage the fetus – thought to occur in as many as 2% of all newborns – include toxoplasmosis, rubella, cytomegalovirus, and herpes simplex. One of the best-known of these is rubella, also known as German measles. If rubella is acquired by the mother during the first month of gestation, the infant has a 50% chance of being mentally retarded (Brosco et al., [2006](#)). Fortunately, this form of intellectual disability has drastically decreased in areas of the world that have programs to vaccinate children against rubella.

Some substances ingested by the mother are toxic to the developing fetus and can cause intellectual disability. The best example of this is alcohol, although other drugs of abuse can also affect brain development. Fetal alcohol spectrum disorders (FASD) are intellectual disabilities caused directly by the mother's consumption of alcohol during pregnancy. On the most severe end of the FASD continuum is fetal alcohol syndrome (FAS), a leading cause of intellectual disability. While the prevalence of FAS in the United States is estimated at approximately 2–7 of every 1,000 children, the broader continuum of FASD is estimated to affect as many as 5% of children in the nation (May et al., [2009](#), [2014](#)). Intellectual impairment due to fetal alcohol exposure is entirely preventable, and thus it is a prime target of public health efforts (Memo et al., [2013](#)).

FAS causes hyperactivity, poor impulse control, social and emotional difficulties, difficulties in learning and memory, and executive dysfunction (for review, see Kodituwakku and Kodituwakku, [2014](#)). Generally speaking, children with FAS show greater cognitive impairments when they are tested on more complex and demanding tasks, and patterns of deficits may become more pronounced at later stages of development, such as adolescence. Secondary to these cognitive effects are increased risks for unemployment and psychiatric disorders in adulthood (Rangmar et al., [2015](#)). Children with FAS also exhibit slowed physical growth (including small head size) and abnormalities of the face and cranium, as shown in [Figure 15.13](#). However, children

with less severe FASD effects may have cognitive deficits without the accompanying characteristic facial features.



Figure 15.13 Physical facial features associated with fetal alcohol syndrome.

Some of these facial features include small eyes, a short upturned nose, and a smooth skin surface (without any indentation) between the nose and upper lip.

Copyright © David Young-Wolff/Photo Edit.

FASD is associated with changes in brain structure, such as reductions in gray-matter volume throughout the brain (Roussotte et al., [2010](#)). The trajectory of white-matter development throughout childhood and adolescence is also delayed in those with FASD, with tracts connecting the frontal lobes with other brain regions especially affected (Treit et al., [2013](#)). It is not well understood what quantity of alcohol ingestion during pregnancy is sufficient to cause symptoms of FAS or less severe conditions on the FASD spectrum, so expectant mothers are often advised to avoid alcohol altogether.

Dyslexia

As we've just seen, intellectual disability describes a condition in which functioning is impaired across a broad range of domains. In contrast, other developmental disorders involve difficulty with acquiring cognitive skills in only one particular domain. When

only one cognitive domain is affected, the condition is referred to as a [learning disability](#). [Dyslexia](#), sometimes referred to as a specific reading disability, is a specific inability to learn to read at an age-appropriate level, despite adequate opportunity, training, and intelligence. Other specific learning disabilities exist as well. For example, children with a nonverbal learning disability have a specific deficit in processing nonverbal material. Much less is known about this disorder, so we do not discuss it in detail here (see Forrest, [2004](#), for a review). Dyslexia is one of the most common learning disabilities, affecting approximately 5–10% of school-age children in the United States, with a higher prevalence among boys than girls (Peterson and Pennington, [2012](#), [2015](#)).

Children with difficulty reading are considered to have dyslexia when they have adequate intelligence to support the cognitive demands imposed by reading, can perform age- and grade-appropriate cognitive functions, and have been exposed to written language and instruction in reading. For example, an 8-year-old child with a specific reading disability would be unable to read but could solve age-appropriate math problems. As the child gets older, however, acquisition of knowledge in other subjects besides written language may be compromised, because knowledge in literate societies is often conveyed via written materials. Simply put, in traditional schooling reading is an essential skill underlying the acquisition of knowledge in many other areas.

Although many people incorrectly assume that the cardinal sign of dyslexia is writing letters backward, dyslexia is generally characterized by a deficit in phonological understanding (Peterson and Pennington, [2012](#), [2015](#)). Phonological processing involves linking a particular letter to a particular sound and being able to parse words into their constituent phonemes, a process sometimes referred to as decoding. For example, to decode the word *chart*, a person must be able to break the word down into separate sound units (ch, ar, t) and to know how those sound units are represented visually. People with dyslexia, in contrast, often learn to read using the whole-word route rather than by breaking words down into phonemes (refer to [Chapter 8](#) for a discussion of different routes in reading). This reliance on visual form, rather

than using the strategy of sounding out words, causes readers with dyslexia to make unusual errors, such as misreading house as “hose.”

Although researchers generally agree that [phonological awareness](#) is disrupted in dyslexia, they are still trying to pin down exactly why it is disrupted. One possibility is that the requisite perceptual mechanisms needed to acquire phonological awareness are deficient. According to this idea, difficulty with the fine temporal analysis of auditory information would prevent people with dyslexia from processing the critical acoustic parameters, such as voicing, that distinguish between phonemes (see Chapter 8, page [230](#); Goswami, [2011](#); Lehongre et al., [2011](#)). Indeed, some evidence suggests that people with reading impairment do have difficulty with certain aspects of auditory processing, particularly in distinguishing the order of sounds presented in close succession (Vandermosten et al., [2010](#)).

Another possibility is that the sounds of words are being adequately represented by the auditory system, but that this information is poorly communicated to higher-level regions involved in language. For example, one study found that adults with dyslexia had similar patterns of primary and secondary auditory cortex activation in response to speech sounds, compared to matched adults without dyslexia, but they differed in the connections between auditory cortex and an inferior frontal region corresponding to Broca’s area (Boets et al., [2013](#)). Specifically, the adults with dyslexia had reduced functional connectivity between the superior temporal region (auditory cortex) and Broca’s area. In addition, structural imaging indicated that the dyslexics have reduced white matter in the left arcuate fasciculus, the fiber pathway that connects temporal and frontal regions within the left hemisphere. Together, these results imply that the major difference between the dyslexic and nondyslexic brains was not in the auditory representation of phonemes, but in the linking of those auditory representations with other language regions.

Although phonological interpretations of dyslexia are currently favored, other researchers have focused on the role of visual processing in dyslexia. Because reading

requires the linkage of sounds to visual symbols, a deficit in visual representation of words, inaccurate perception of visual forms during the eye movements involved in reading, or disrupted visuospatial attention could potentially lead to difficulty in reading (see Sperling et al., [2005](#); Stein et al., [2000](#); Vidyasagar and Pammer, [2010](#)). It may be that reading difficulties can arise from more than one source, meaning that these explanations for dyslexia are not mutually exclusive (Peterson and Pennington, [2015](#)).

Functional imaging studies generally implicate the left perisylvian regions in dyslexia. A recent meta-analysis found that during language processing tasks, people with dyslexia tend to show less activity than controls in the left perisylvian area, a region that includes language-related areas around the Sylvian fissure that are adjacent to but separate from those involved in the initial processing of sound (Richlan et al., [2009](#)). The meta-analysis also found underactivation of the visual word form area (VWFA), a ventral stream visual processing region that is typically engaged during reading (see [Chapters 6](#) and [8](#)). Functional connectivity among brain regions such as the VWFA and perisylvian regions is also disrupted in people with dyslexia, consistent with the idea that dyslexia involves disconnections between critical language regions, in this case linking visual symbols to phonology (e.g., Finn et al., [2014](#)).

Like many conditions, dyslexia is heritable, and neural abnormalities have been identified in children who are at risk for dyslexia based on family history, even before the age when they begin to read (e.g., Raschle et al., [2011](#); Skeide et al., [2016](#)). Numerous genes have been linked to dyslexia, and in most cases the genes appear to influence neuronal migration and axon growth (Carrion-Castillo et al., [2013](#); Galaburda et al., [2006](#); Scerri and Schulte-Körne, [2010](#)). Therefore, one possibility is that due to genetic factors, cell migration in particular areas of the cortex is disrupted, leading to dyslexia. Abnormalities in cell migration are known as ectopias, and are evident in the perisylvian region in dyslexia (see [Figure 15.14](#)). It is not known, however, why abnormal migration would be restricted to the perisylvian region or exactly how it might contribute to the cognitive function of phonological awareness that seems to be at the heart of dyslexia.

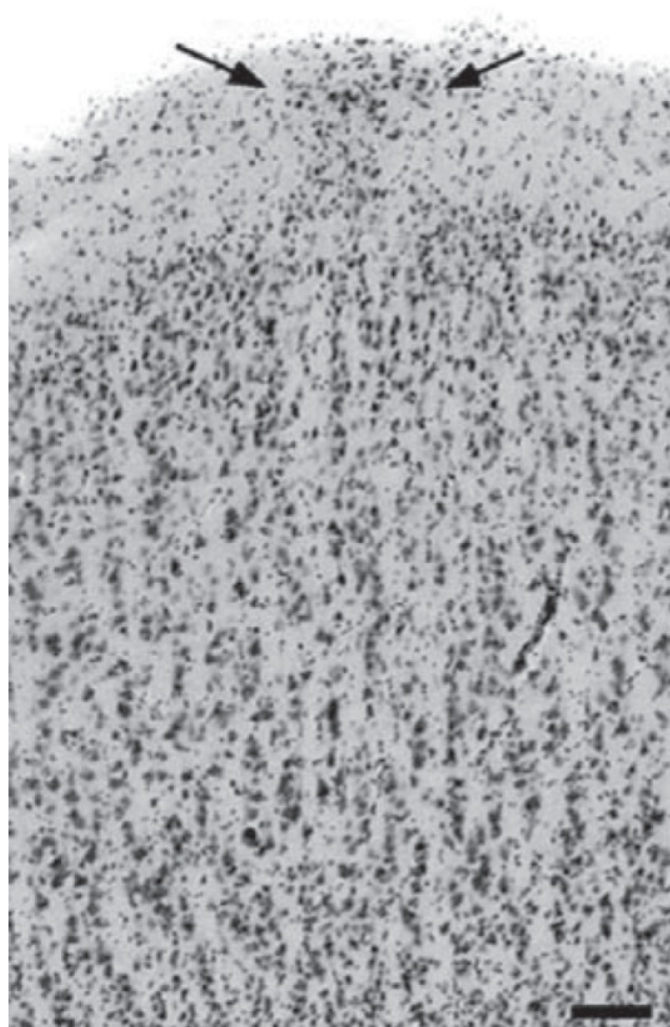


Figure 15.14 An ectopia, or abnormality of cell migration, in layer I of the cortex in a dyslexic individual.

Source: Figure 2 from Galaburda, A. M., et al. (2006). From genes to behavior in developmental dyslexia. *Nature Neuroscience*, 9, 1213–1217. Adapted by permission from Macmillan Publishers, Ltd.

Before leaving the topic of dyslexia, we note that reading disability is an area where brain and culture meet. Children with difficulty in phonological awareness are especially challenged by languages such as English, in which there is no clear one-to-one correspondence or mapping between letters and sounds. (For example, in English, “f” and “ph” are linked to the same sound.) These difficulties are somewhat reduced in a language such as Italian, which has regular and consistent mappings between sounds and symbols (Ziegler and Goswami, 2005). Interestingly, though, a classic study found

that dyslexic readers of Italian, French, or English exhibit a similar pattern of neural activation – decreased activity in the left posterior temporal region – regardless of their language (Paulesu et al., [2001](#)). This finding indicates that even though people with dyslexia may be less likely to display reading difficulties in one language, such as Italian, than another, such as French or English, the neural substrate that supports reading is altered in similar ways. This finding has been supported by meta-analytic examination of subsequent studies (Martin et al., [2016](#)). In other words, the neural underpinnings of dyslexia appear to be universal across different languages. In [Chapter 17](#), we return to dyslexia as an example of a research area in which increasing knowledge from cognitive neuroscience may have implications for aspects of education.

Autism

We first encountered autism in [Chapter 13](#) when covering the topic of social cognition, which is disrupted in autism. Here, we extend our coverage of autism more broadly to consider autism in the context of developmental disorders. As we discussed in [Chapter 13](#), a diagnosis of autism spectrum disorder according to the DSM-5 involves two main characteristics: (1) impairment in social interaction across a range of contexts, such as deficits in social reciprocity, nonverbal communicative behavior, or development of social relationships; (2) restrictive or repetitive activities or interests, including repetitive motor actions (stereotypies such as hand-flapping), fixated narrow interests, inflexibility in the face of changes in routine, and/or hyper- or hyposensitivity to sensory information in the environment (American Psychiatric Association, [2013](#)). When symptoms occur alongside relatively high levels of intellectual functioning, the person is often described as having Asperger syndrome, although this is no longer an official diagnostic label in the DSM, psychiatrists' standardized framework for making diagnoses.

You may have first heard about autism through news reports suggesting that autism is on the rise and that vaccines given in childhood may contribute to the disorder. Although diagnosed cases of autism did appear to rise in the 1990s and 2000s, evidence suggests

that increased public knowledge about the disorder, along with more liberal diagnostic criteria, largely account for this apparent increase (Baio, [2012](#); Gernsbacher et al., [2005](#)). For example, one study supporting this view found that diagnoses of autism in California were clustered in geographic areas that had more resources for diagnosis and treatment (Mazumdar et al., [2013](#)). Although estimates vary, autism occurs at a rate of about 5–10 cases per 1,000 children (e.g., Baio, [2012](#); Baxter et al., [2015](#); Elsabbagh et al., [2012](#)).

Moreover, contrary to popular opinion in some quarters, vaccines do not appear to cause or contribute to autism. A recent study of over 95,000 American children found no association between autism and exposure to the childhood measles-mumps-rubella vaccine (Jain et al., [2015](#)). Likewise, a study that focused on more than 250 children with autism found that they had no different exposure to vaccines than nonautistic control children matched in age and sex and drawn from the same health-plan database (DeStefano et al., [2013](#)). These studies confirm the results of earlier epidemiological studies indicating no association between autism and vaccines (e.g., Hviid et al., [2003](#); Madsen et al., [2003](#); Stehr-Green et al., [2003](#)). Furthermore, an experimental study in infant monkeys found that administration of vaccines containing the ingredient thimerosal, which is a common preservative used in vaccines to prevent potentially life-threatening contamination with harmful microbes, had no effect on the monkeys' behavior nor did it produce any pathological effects in the monkeys' brains (Gadad et al., [2015](#)). Rather than being caused by vaccines, as some fear, autism appears to be a heterogeneous disorder with many potential causes, including genetic disorders, infectious diseases, birth injuries, metabolic diseases, and environmental factors (e.g., de Rubeis et al., [2014](#); DiCicco-Bloom et al., [2006](#); Krakowiak et al., [2012](#); Jiang et al., [2016](#); Lyall et al., [2014](#); Sandin et al., [2012](#)).

Autism is considered a developmental disorder because its characteristics are evident in childhood. In fact, one of the key DSM-5 requirements for a diagnosis of autism is that symptoms must be present in early development. Most children with

autism receive a diagnosis around the age of 3 years, although behavioral signs are often evident earlier (Barbaro et al., [2009](#); Costanzo et al., [2015](#); Zwaigenbaum et al., 2013). For example, one longitudinal study in the UK followed more than 14,000 children whose mothers were pregnant in 1991–1992 (Bolton et al., [2012](#)). The researchers determined whether the children were diagnosed with autism by the age of 11, and then went back and looked at how their parents described them at the time when they were infants and toddlers. Children who were later diagnosed with autism showed differences from typical children according to their parents' reports within the first year of life, particularly with regard to social and communication behaviors. Children who later received a diagnosis of autism were also reported by their parents to engage in more repetitive play by the age of 2 years. Studies such as these indicate that autism is a very early-developing condition, even when it is not officially diagnosed until later.

What, then, is different about brain development among those with signs of autism? One clue is that overall brain volume early in life is enlarged in people with autism (see [Figure 15.15](#)). For example, one prospective study assessed brain volume in infants known to be at high risk for developing autism based on having a sibling with the condition (Shen et al., [2013](#)). Infants who later were diagnosed with autism had enlarged brain volumes at both 12–15 and 18–24 months of age, compared to high-risk infants who did not later develop autism (see also Schumann et al., [2010](#)). Complicating this picture, however, other research has found that autism-related differences in cortical thickness depend on age, with increased cortical thickness (relative to nonautistic peers) early in development, followed by decreased thickness in later years of development (Zielinski et al., [2014](#)). Likewise, studies of white-matter development have found that children with autism have increased white matter early in development, followed by a slower rate of myelination such that they later fall behind their peers in white-matter development (Wolff et al., [2012](#)). Together, these results remind us that developmental differences, such as those seen when comparing autism to typical development, can take the form of altered trajectories over time, rather than being

reduced to a simple story of “too much” or “too little” of some neural process or brain region.

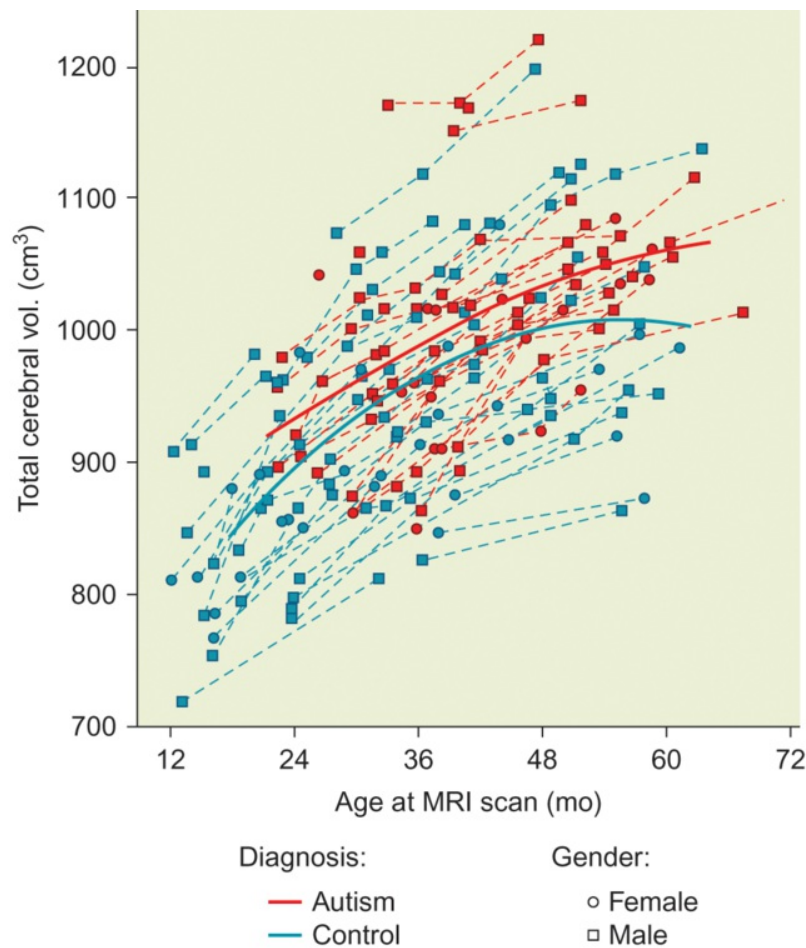


Figure 15.15 Increased brain volume during the first years of life among children diagnosed with autism (red line) compared to typically developing controls (blue line).

Squares represent boys and circles represent girls.

(from Schumann et al., [2010](#))

Researchers are still working to piece together the puzzle of how early-life alterations in brain development contribute to the pattern of cognitive deficits that characterize autism. As we reviewed in [Chapter 13](#), people with autism often have difficulty understanding the mental states of others, perceiving the emotional expressions of others, and interpreting subtle social cues. Some research has found

differences between people with and without autism in activation of neural mechanisms thought to support these skills, such as the mirror neuron system, regions involved in “mentalizing,” and face processing regions in the ventral stream (see [Chapter 13](#)). Future research is needed to better understand how these differences in regional brain activity and function arise from altered developmental trajectories early in life.

Attention-Deficit/Hyperactivity Disorder

[Attention-deficit/hyperactivity disorder \(ADHD\)](#) is a developmental disorder in which the affected child is either inattentive, hyperactive/impulsive, or both, compared to the average child of the same age (American Psychiatric Association, [2013](#); see Thapar and Cooper, [2016](#), for review). These children can be capable of paying attention and sitting still, as they may spend hours playing a video game, but overall their ability to pay attention is much less than is typical for children their age, and they are often guided by environmental dependencies similar to those discussed in [Chapter 11](#). ADHD is estimated to affect about 8–10% of all children in the United States, with boys more often diagnosed with the condition than girls (Feldman and Reiff, [2014](#); Thomas et al., [2015](#)). Although most commonly considered to be a disorder of childhood, ADHD may not be diagnosed until a person reaches adolescence or adulthood (Volkow and Swanson, [2013](#)). Invariably, however, the behaviors associated with ADHD will have been present since childhood.

Many people have expressed concern about the potential overdiagnosis of ADHD, particularly because some of its symptoms seem like common childhood behavior, such as fidgeting and difficulty in controlling impulses. To protect against labeling normal behavior as disordered, the DSM-5 diagnostic criteria require that the symptoms must be “inconsistent with developmental level” and that the child must have a clinically significant impairment that interferes with adaptive functioning in more than one setting (e.g., both school and home).

Not surprisingly, ADHD often impedes a child's progress in learning, especially in a structured environment, because the child's impulsivity and distractibility do not allow him or her to sit still long enough to absorb material or to listen to instructions. If impulsive behavior leads to difficulty with peers and authority figures, the risk for engaging in antisocial behavior rises. Moreover, although ADHD is a distinct condition, it regularly co-occurs with other learning disabilities such as dyslexia.

Although the name "attention-deficit disorder" implies that researchers have a clear idea of the cognitive difficulty – a deficit in attention – there is disagreement in the literature about the core deficit in ADHD. One idea is that arousal mechanisms dependent on norepinephrine are disrupted in people with ADHD, leading to difficulty in sustaining attention over long periods of time (Huang-Pollock et al., [2012](#); Sergeant, [2005](#)). To assess sustained attention, researchers often use tasks such as the continuous performance task. In this task, the participant must respond to a certain stimulus anytime it appears; for example, pressing a key anytime an "X" appears in a continuous stream of letters. Typically, the task goes on for a long time, and the time delay between letters can be long. Thus, quick and accurate responses require the ability to sustain attention and arousal even when things get boring. While there has been some controversy about how consistently children with ADHD exhibit deficits on such tasks (Karatekin, [2001](#)), recent evidence suggests that such deficits are quite good at distinguishing ADHD children from their unaffected peers (Berger et al., [2017](#)).

Another idea is that people with ADHD have a core deficiency in inhibitory control. Indeed, one of the most reliably observed effects in ADHD is the inability to inhibit inappropriate responses (Barkley, [1997](#)). Intuitively, behavioral inhibition seems naturally linked to ADHD, because such children often appear to act impulsively. To measure inhibitory control in the lab, researchers often use a task such as the stop-signal task (Logan et al., [1984](#); Verbruggen and Logan, [2008](#)). In this task, participants are trained to make a particular response to a particular stimulus; for example, press the right key when a circle appears, and the left key when a square appears. However,

during some trials, just after the target item appears, participants are given a signal, such as a “beep,” that indicates not to respond on that trial. Numerous studies have found that children with ADHD have particular difficulty overriding or aborting the prepared responses on the “stop” trials (e.g., McAuley et al., [2014](#); Wright et al., [2014](#)). Such inhibitory deficits are likely to reflect more general difficulties in executive control (Willcutt et al., [2005](#)).

Yet another theory argues that children with ADHD have a specific deficit in certain aspects of motivational processes, such as an unwillingness to wait for rewards, often referred to as delay aversion (Sonuga-Barke et al., [2008](#)). For example, children with ADHD are biased (even more so than children without ADHD) to choose an immediate reward that is smaller than a larger reward that they must wait to receive.

Brain imaging provides some evidence of alterations in brain regions that support each of these processes: sustained attention, executive function, and delay aversion. First, researchers have identified a pattern of connectivity across the brain at rest that predicts variation in how well people perform on a sustained attention task (Rosenberg et al., [2016a](#)). These connectivity patterns involve linkages between a large set of brain regions spanning from subcortical to thalamic to cortical regions, all of which play a role in sustained attention (see [Chapter 10](#)). Alterations in this network can predict the severity of symptoms observed in ADHD (Rosenberg et al., [2016a](#)). Moreover, when adults with ADHD are given methylphenidate, a common treatment for ADHD, their resting-state pattern of connectivity normalizes to more greatly resemble patterns of connectivity associated with high degrees of sustained attention (see [Figure 15.16](#); Rosenberg et al., [2016b](#)).

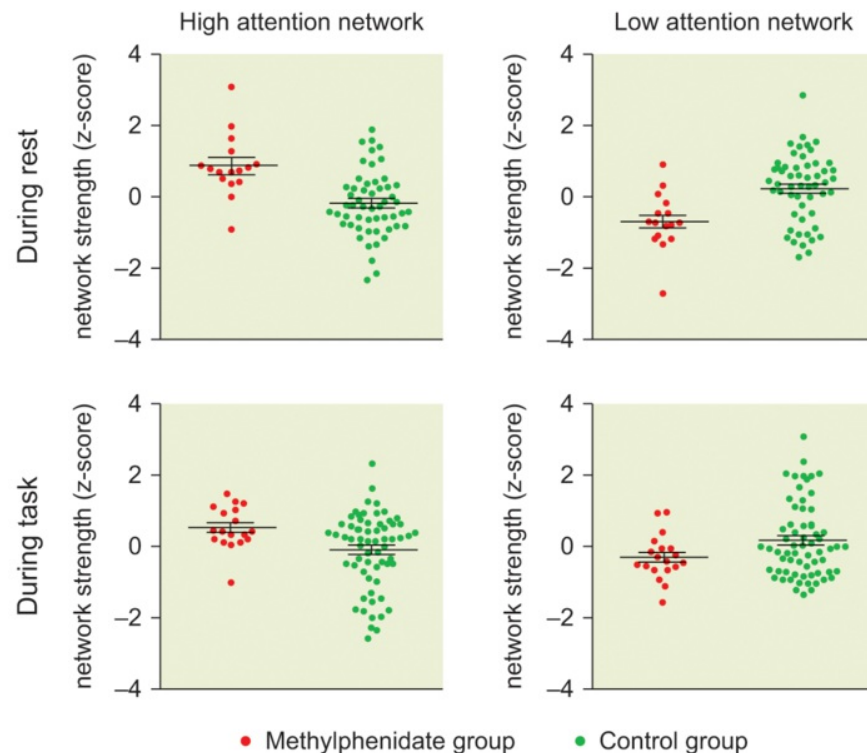


Figure 15.16 Effects of methylphenidate on attention networks.

Treatment with methylphenidate, a drug often used to treat ADHD, increases activity in a network associated with higher performance on an attentional task (left-hand panel), and decreases activity in a network associated with lower performance on an attentional task (right-hand panel). Activity was measured during performance of a task of inhibitory control, and each circle on the figure represents one participant in the study. On average, participants in the methylphenidate group showed increased activity in a high-attention network, and lower activity in a low-attention network, compared to the control group.

(from Rosenberg et al., [2016b](#))

There is also clear evidence of disrupted functioning of networks involved in executive aspects of attention in people with ADHD. During a variety of executive tasks, ranging from those that require inhibition of motor responses to those requiring task-switching, people with ADHD exhibit alterations in dorsolateral and ventrolateral prefrontal cortex as well as the basal ganglia, all regions associated with executive control (see [Chapter 10](#)) (Rubia, [2011](#)). In addition, meta-analyses indicate reliable

reductions in activation of right ventrolateral (i.e., inferior) frontal regions, as well as alterations in activation in portions of the basal ganglia, during inhibitory control tasks in people with ADHD (Cortese et al., [2012](#); McCarthy et al., [2014](#); Norman et al., [2016](#)) as well as alterations in activation of portions of the basal ganglia (Cortese et al., [2012](#)). Moreover, treatment with stimulant drugs is associated with enhanced activity in the right inferior frontal cortex (Rubia et al., [2014](#)). Finally, supporting the delay aversion hypothesis, meta-analyses indicate that, across studies, people with ADHD show hypoactivation of the basal ganglia in anticipation of rewards (Plichta and Scheres, [2014](#)).

You may remember from prior chapters that dopaminergic cells project both to the basal ganglia and prefrontal cortex, regions whose activity is altered in ADHD. In fact, the brain's dopaminergic system is strongly implicated in ADHD. The drugs that are used to treat ADHD are known to influence the dopamine system, and these drugs have a beneficial effect on cognitive performance in children with ADHD (see Heal et al., [2012](#), for review). Medications used to treat ADHD include those derived from amphetamine (trade names: Dexedrine, Adderall), methylphenidate (trade name: Ritalin), atomoxetine (trade name: Strattera), and Bupropion (trade name: Wellbutrin). Methylphenidate, for example, affects the dopaminergic neurotransmitter system by slowing the rate of dopamine reuptake on postsynaptic sites.

ADHD has a strong genetic component, and candidate genes implicated in relationship to ADHD are generally genes that influence dopaminergic neurotransmission. Such genes include the dopamine receptor genes (e.g., DRD_1 , DRD_4); the COMT gene, which influences dopamine metabolism; and the dopa decarboxylase gene, which is crucial for dopamine synthesis (e.g., Albrecht et al., [2014](#); Franke et al., [2012](#); Waldman and Gizer, [2006](#)). Because frontal and striatal regions are heavily innervated by dopamine pathways, genetic differences in dopamine metabolism in ADHD fit with findings of anatomical and functional differences in the frontal-striatal regions in ADHD. However, recent studies also implicate other genes involved in neural development (e.g., Middeldorp et al., [2016](#); Stergiakouli et al., [2012](#)), indicating

that a solely dopamine-based explanation is unlikely to completely account for the development of ADHD.

In addition to the typical treatment for ADHD, which involves the administration of medication, researchers have also explored behavioral interventions (e.g., Pelham and Fabiano, [2008](#)). Typically, such programs involve working with parents and teachers to better manage the child's behavior at home and in the classroom. Benefits may be obtained from behavioral treatments (Daley et al., [2014](#)), but studies that have directly compared medication and behavioral treatments find medication to be more effective on average (e.g., MTA Cooperative Group, [1999](#)). In most cases, a combination of medication and behavioral modification strategies is recommended (Feldman and Reiff, [2014](#)).

Before we leave the topic of developmental disorders, it is important to consider what happens when these children become adults. For some of the disorders we have discussed, the outcome is relatively straightforward. For instance, people who exhibit general intellectual disability as children also exhibit intellectual impairment as adults. But what about some of the more specific learning disabilities, such as dyslexia and ADHD? Do children outgrow these disorders, or are they impaired for life?

One theory, the [maturational lag hypothesis](#), postulated that people with specific learning disabilities are slower to mature than their peers, and that with time they will outgrow the problem much the way that children are thought to shed baby fat. This idea was fueled in part by observations that learning disabilities appear to become less severe with age in certain subpopulations of children. For example, some children with ADHD appear to become less impulsive around the age of 12 years, which is when children typically show an increase in attentional abilities. However, difficulties appear to manifest in a different form and manner as an individual matures. For example, at age 12 a child with ADHD may be able to sit in his chair in a classroom, something he could not do at age 7, but he may still have an inability to “sit with” a homework problem.

While the developmental pattern by which the brain matures during childhood and

adolescence does appear to differ between individuals with ADHD and those without (e.g., Shaw, Lerch et al., [2006](#); Shaw et al., [2013](#)) and those patterns may affect adult outcomes, the idea that these learning disabilities miraculously disappear at adulthood is unlikely. In fact, this is nicely illustrated by a study in which over 2,000 college students were screened to find two dozen of the most able of those with a confirmed diagnosis of ADHD starting in childhood (Banich et al., [2009](#)). Importantly, these students did not have any other comorbid disorders that sometimes accompany ADHD, such as learning disabilities. In addition, they were matched to control participants on a variety of measures including age, gender, and IQ. Therefore, if any differences were observed between the groups, it was most likely driven by whether or not an individual had ADHD.

When given a task of executive processing, the Stroop task, the college students with ADHD showed reduced activation in dorsolateral prefrontal cortex as compared to controls (Banich et al., [2009](#)). They also exhibited reduced prefrontal activation during a task that required inhibition of memory retrieval, and showed poorer performance on motoric tasks of inhibitory control, such as the stop-signal task (Depue et al., [2010b](#)). Nonetheless, consistent with the idea that ADHD involves alterations in multiple brain regions, the severity of ADHD symptoms was predicted not just by activation in dorsolateral prefrontal cortex, but also by many other brain regions, most of which receive dopaminergic innervation (Depue et al., [2010a](#)).

While these studies suggest that one cannot outgrow ADHD, at the same time, it is important to remember that many people with dyslexia, ADHD, and other learning disabilities go on to have successful personal and professional lives, probably by emphasizing other cognitive strengths. As we learn in the next sections, the brain has great potential for reorganizing in response to trauma and deprivation. This plasticity may account for some of the diminution in learning disabilities that can occur as a child ages. We now turn to an examination of the reorganization and plasticity of the brain.

Brain Plasticity in Adulthood

So far we have focused on the development of the brain and on disorders in neuropsychological development. However, the brain is not rigidly fixed in adulthood. Logically, this must be true at some level; after all, if the brain were incapable of change at the time of adult maturation, you would never be able to learn a new skill or modify your way of thinking! At a minimum, we know that adults can learn (yes, you can teach an older dog new tricks). Therefore their brains can respond to environmental input – that is, they can change. We also know that, contrary to long-standing dogma, new neurons are generated even in adulthood, though certainly not at anywhere near the rate of neurogenesis in the perinatal period. We have already discussed the basic mechanisms of learning and memory in [Chapter 9](#), so here we focus on additional issues related to plasticity in adulthood.

Numerous studies have shown that increased experience in adulthood can lead to changes in the representation of information in the brain. For example, training monkeys to distinguish between particular line orientations led to fine-tuning of the receptive fields for the cells coding those orientations in primary visual cortex (Schoups et al., [2001](#)). In humans, learning to juggle in adulthood led to a growth in the size of visual area MT, which participates in coding for visual motion (Draganski et al., [2004](#)). The increase in MT size was not maintained when participants stopped juggling for a few months, however, illustrating the “use it or lose it” phenomenon. Similarly, learning to play professional handball is associated with increased gray matter in motor and somatosensory regions, with the largest increases occurring among the players who started playing at the youngest ages (Hänggi et al., [2015](#)).

All these examples suggest that training strengthens cortical representations – but what happens when input of a certain kind is lost? Do representations wither away? Research with other species suggests that the answer is yes. Some research has investigated how the representation of the hand and fingers in somatosensory cortex changes after amputation or nerve damage (Kaas, [2000](#); see also Xerri, [2012](#); Sammons and Keck, [2015](#), for examples in the visual modality). As you may remember from

[Chapter 1](#), the somatosensory cortex includes a map of the body, in which each section of the map consists of cells responsive to sensation from a distinct part of the body. When sensation from a particular body region is consistently missing, as in the case of an amputation, the map in somatosensory cortex is reorganized, such that the territory previously corresponding to that lost part is now responsive to a neighboring part of the body (i.e., a nearby finger) (see [Figure 15.17](#)). This research tells us that the “maps” that exist in our sensory cortices are not set in stone, but rather that they are maintained only through continual sensory input. When input changes systematically, the map changes. This change in cortical maps or the function of a brain region is referred to as [reorganization](#).

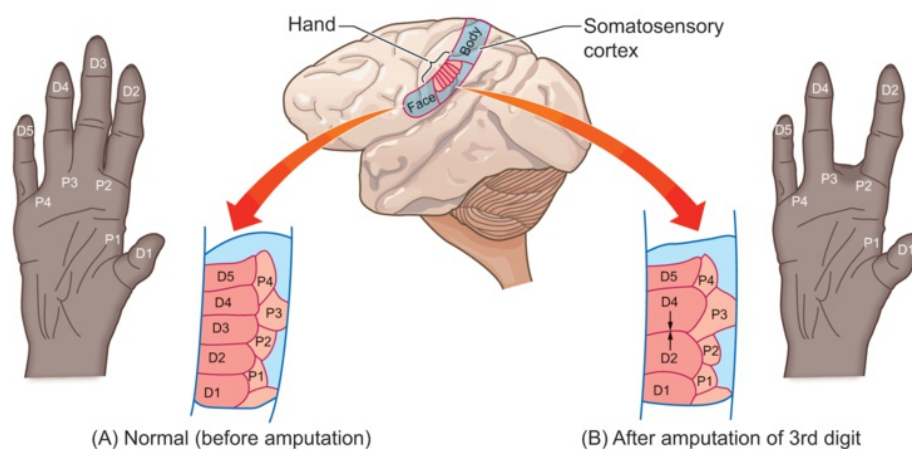


Figure 15.17 Somatosensory cortex reorganizes after amputation.

The region of somatosensory cortex that represents the hand surface changes after a monkey's finger is amputated. The region that used to represent the amputated finger begins to represent information from neighboring fingers and the palm surface.

These research findings have been applied to try to understand phantom sensations in people who have lost limbs. Even though they know that the limb is gone, some amputees continue to perceive sensations from the missing limb, and these sensations can be distracting and even painful. Some researchers have suggested that phantom limb sensations are elicited when cells that used to code for the lost limb are now being

stimulated by new input from a different body location (Ramachandran and Hirstein, [1998](#); see also Flor et al., [2006](#); Makin et al., [2015](#)) (see [Figure 15.19](#)). Because of this transition in the cells' coding – they used to code for one body part, but now code for another body part – phantom sensations may arise.

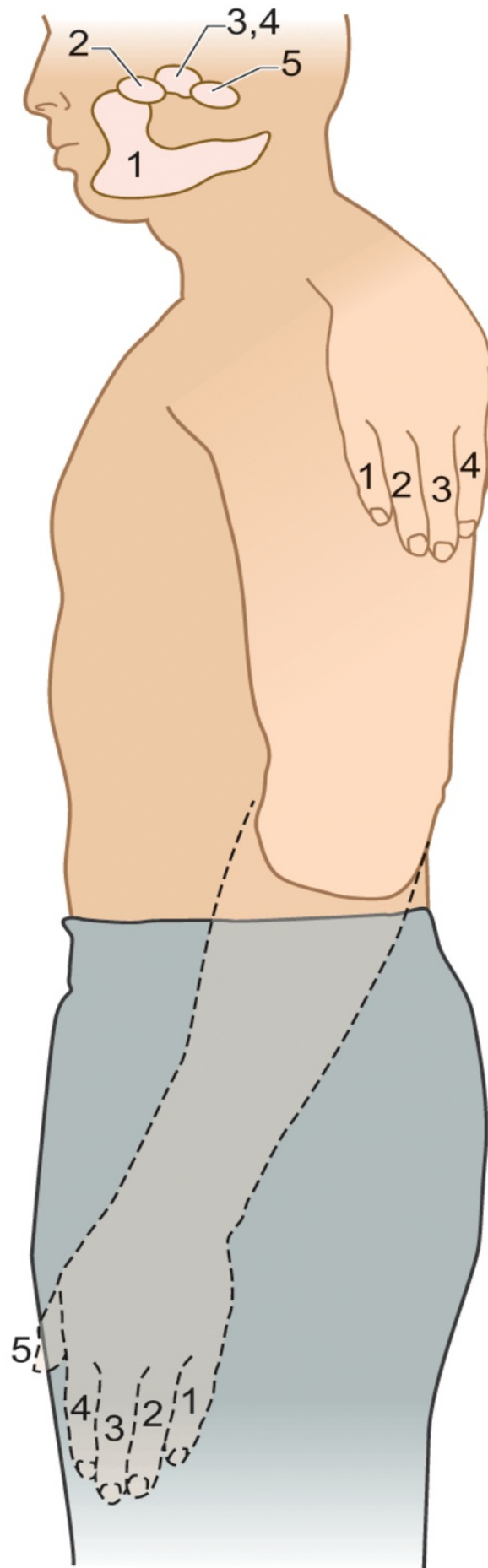


Figure 15.18 Phantom sensations in an amputee.

For an amputee who has lost the lower part of one arm, stimulation of certain regions of the face may give rise to phantom sensations in the (missing) fingers (numbered 1 through 5). Stimulation of the shoulder area may also give rise to phantom sensations in the fingers.

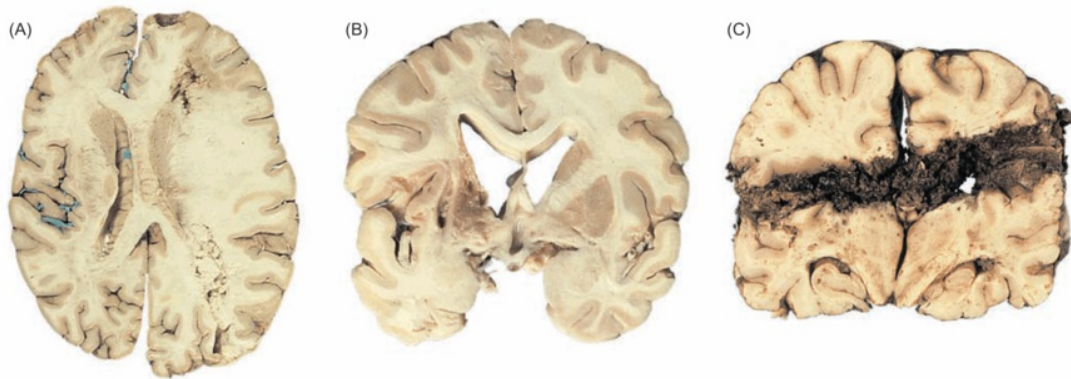


Figure 15.19 Types of damage to the human brain.

(A) Brain following a stroke that caused severe swelling on the right side of the brain. (B) Brain following a stroke that left cavities of lost cells on the left side. (C) Brain of a person who suffered a gunshot wound.

Courtesy of Dr. Dana Copeland.

How dramatic can reorganization be? The examples we have just discussed pertain to reorganization on a relatively small scale, within a map in one sensory cortical region. But what if the person loses an entire sensory modality altogether? When a person loses vision or hearing, either at birth or later in life, what happens to the cortical regions that would normally respond to sight or sound? Several studies have found that congenital blindness leads to reorganization of the “visual” cortex for other functions. For example, in congenitally blind people, the “visual” cortex is activated by Braille reading and other tactile stimulation, as well as by some auditory and verbal tasks (e.g., Amedi et al., [2003](#); Burton et al., [2004](#); Röder et al., [2002](#); see Kupers and Ptito, [2014](#), for review). This evidence indicates that the “visual” cortex can reorganize

to respond to nonvisual information in congenitally blind people, a phenomenon known as [cross-modal plasticity](#).

Cross-modal plasticity can be evident even with changes in sensory input in adulthood. For example, several studies have found that “visual” cortex is activated by Braille reading in people who became blind later in life (Burton et al., [2002a](#), [2002b](#)). Other research has found that even among sighted people who learn Braille, the visual cortex responds to tactile sensations during Braille reading (Siuda-Krzywicka et al., [2016](#)). These results imply that repurposing of visual cortex to support processing in other sensory modalities can occur in adulthood, not just in response to congenital loss of vision. (See also the “In Focus” feature in this chapter, which discusses enhanced abilities in those who have lost a sensory modality.)

Another way of asking the plasticity question is to examine whether the cortex can reorganize when a sensory modality is restored. Imagine a person who was born blind or deaf due to defects in the eye or ear, but then later received a treatment that restored sensory input. For example, a person who was born with cataracts had those cataracts removed later in life; or a person who was born profoundly deaf, because of problems with the inner ear, but was later given cochlear implants that stimulate the auditory nerve.

There is currently much debate about the extent to which normal sensation can be restored in adulthood in such patients. Experimental studies with animals suggest that when sensory input is restored, the cortex associated with the sensory modality responds to such input. For example, in congenitally deaf cats, implantation of cochlear implants can elicit responses to auditory stimulation in the auditory cortex (Klinke et al., [1999](#); Land et al., [2016](#); Moore and Shannon, [2009](#)). Similarly, treatment of a defect in a dog’s retina with gene therapy leads to a response to visual information in the dog’s visual cortex, even when the treatment occurs as late as ages 1 to 4 years (Aguirre et al., [2007](#)), which would be about the equivalent of 15 to 40 years of age in humans.

These studies imply that the relevant cortical regions still maintain some ability to respond to restored sensory input. But how well do these systems function? In clinical practice, cochlear implants to restore hearing in deaf children are most beneficial when implanted early in life (Copeland and Pillsbury, [2004](#); Kral and O'Donoghue, [2010](#); Moore and Shannon, [2009](#)). For example, one study found that spoken language development was better for children who received cochlear implants before the age of 2.5 years, compared to those who received the implants between 2.5 and 5 years of age (Tobey et al., [2013](#)). For adults who have been deaf since early life, cochlear implants are not typically successful in restoring perception of speech, most likely both because a sensitive period for learning speech sounds has passed and because it is difficult to establish knowledge of speech patterns with the impoverished input from an implant. In the visual domain, rare case studies of previously blind people whose visual input was restored in adulthood report that visual perception is abnormal (Fine et al., [2003](#); Levin et al., [2010](#); Sacks, [1995](#)), although some improvement may be possible following restoration of visual input (Kalia et al., [2014](#)).

Thus, the possibility of recovery of perceptual function can be seen as a glass half-full or a glass half-empty: the adult cortex retains some ability to respond to sensory input even following severe deprivation of that sensory modality, but there are limits to that plasticity. Because the organization of the cortex has been affected by the prior experiences that have lacked information in that specific sensory modality, it is no longer optimally organized to process information in that modality. This example shows how experience interacts with the biological organization of the brain to influence brain functioning.

Recovery of Function Following Brain Damage

In the [previous section](#), we considered the plasticity of the adult brain in response to changing sensory input and experiences. Another kind of question is also important: How does the brain respond to damage? When the brain sustains a specific insult, such

as a gunshot wound or stroke (see [Figure 15.19](#)), what is its capacity for reorganization and recovery? These issues are important not only for enriching our basic understanding of the brain's dynamic nature, but also for providing information that is clinically relevant to the many people who suffer brain damage. First, we describe, in a general manner, the brain's responses to injury on a neurophysiological level. We then discuss the possible mechanisms for recovery. Finally, we compare the differences in recovery of function between adults and children.

Neurophysiological Responses to Insult

Damage to the brain sets a number of physiological processes in motion, some of which occur directly at the site of the lesion and others of which occur at more distant points. [Figure 15.20](#) provides an overview of these physiological processes and the time frame over which they occur. At the site of the lesion, cells begin to die, a process called [necrosis](#). This process affects not only neurons, but also the glia that insulate neurons. In some cases, cell loss may extend past the actual site of damage to more distal neurons, a process called [transneuronal degeneration](#). Such degeneration occurs because neurons require an optimal level of stimulation as well as certain chemical factors from other nerve cells. If a substantial proportion of a neuron's inputs are damaged, that cell may die. Transneuronal degeneration can occur across more than one synapse, having a domino-like effect. For example, if the optic nerve is cut, cells of the lateral geniculate body degenerate completely. Then, as the lateral geniculate begins to degenerate, cells in the visual cortex may degenerate as well. Often transneuronal degeneration is accompanied by accumulations of calcium, a process known as [calcification](#), which is easily detected by brain imaging techniques.

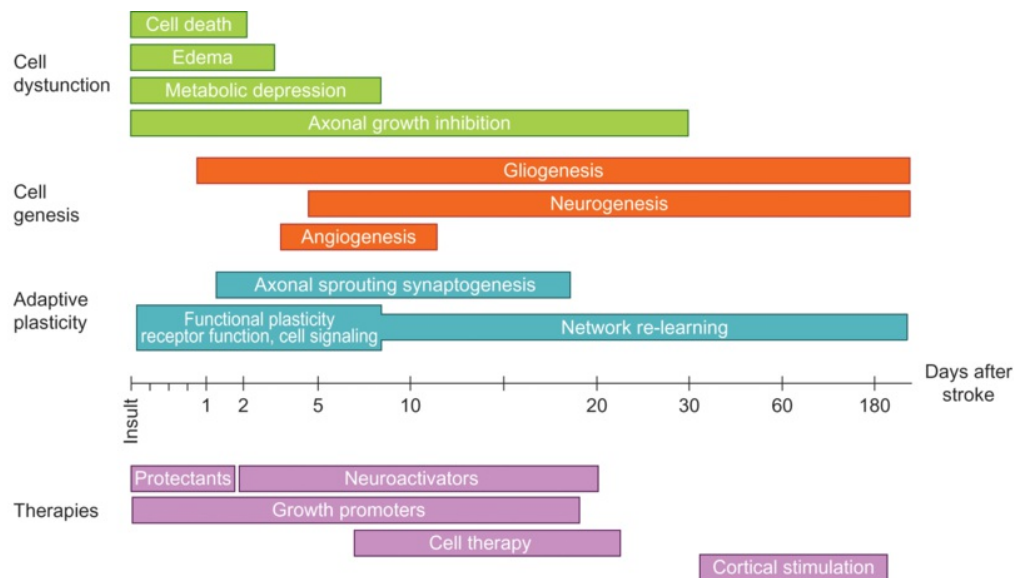


Figure 15.20 Overview of neurophysiological responses to brain injury.

In the first days after a stroke, dysfunctional responses at the cellular level include cell death, edema (swelling), depression in metabolism, and inhibition of axonal growth. Beginning within a few days are processes of cell genesis, including generation of glial cells and nerve cells, and development of new blood vessels (angiogenesis). Longer-term adaptive effects also include sprouting of axons, formation of new synapses, changes in receptor function, and reestablishment of connections among networks of neurons. Different therapies may be undertaken at various stages to protect against dysfunctional cellular responses to injury and to promote adaptive cellular and systems-level responses.

Source: Figure 1 from Wieloch, T., and Nikolich, K. (2006). Mechanisms of neural plasticity following brain injury. *Current Opinion in Neurobiology*, 16, 258–264.

Reprinted by permission of Elsevier.

Dead cells are engulfed and broken down (a process known as phagocytosis) by astrocytes and microglia. Because neurons have a far more limited capacity to regenerate than other cells in the body, fluid now fills the spaces where cells once resided. New capillaries may form in the region as well. The process of phagocytosis and capillary formation may continue for several months until only glial cells remain, a process known as **gliosis**. Astrocytes mark off the region, forming a scar.

In addition to changes in the neurons themselves, other processes occur with damage. One of these, [edema](#), is the swelling of tissue after trauma, which occurs in the brain just as it does in any other part of the body (see [Figure 15.19A](#)). Swelling of the brain involves special dangers. When other body parts swell, they just take up more space under your clothing. But the brain and cerebrospinal fluid share a confined space within the skull; when the brain is bruised, the situation is like having a badly bruised toe that must be shoved into your shoe. The edema associated with brain trauma leads to an increase in intracranial pressure, because more fluid now occupies the same amount of space. This increased pressure can interfere with neuronal function not only at the site of damage, but elsewhere as well. When the edema exerts pressure on brainstem regions controlling vital functions, it can cause a person to become comatose or even die. Therefore, medications and other treatments are given after cerebral trauma to help reduce edema. Because edema may last for some time, the behavioral consequences of a lesion may not become apparent until after the swelling subsides. In addition to these changes, some of the basic aspects of the brain's functioning, such as its metabolic rate, neurotransmitter release, and oxygen consumption, may also be disrupted by a lesion. Although there may be an initial increase in metabolism right after an injury, this is followed by a period of decreased metabolism (Bergsneider et al., [2001](#); Wieloch and Nikolich, [2006](#)).

Given these multiple changes in brain function in response to injury, and the long time span during which they manifest themselves, you can appreciate why a clinician often cannot immediately assess the degree of damage sustained from an injury. If swelling is extensive, the person may show severe impairments at first but significant improvement as the edema decreases. In contrast, responses immediately after oxygen deprivation may lead one to overestimate later levels of functioning, because the detrimental effects of the oxygen deprivation continue to accrue over the time since injury. Thus, the person's behavior immediately after injury only crudely predicts the prognosis for functioning a month or even a year into the future.

Following the acute phase of cell death and dysfunction, a number of changes at the

cellular level may aid in recovery of function (Wieloch and Nikolich, [2006](#)). [Figure 15.20](#) illustrates the timeline of some of these processes. Understanding cellular mechanisms of recovery is important because new medical treatments might be able to stimulate those mechanisms to enhance recovery. One major cellular process is the generation of new cells, both neurons and glia. New blood vessels also grow, a process called angiogenesis, reestablishing blood supply to the damaged region. In addition, new axons begin to sprout, connecting regions that had not previously been connected, and new synapses form.

One possible means by which [regeneration](#) and sprouting may occur is through a substance known as nerve growth factor (NGF), which is transported to nerve cells from glia. Neuroscientist Rita Levi-Montalcini and her colleagues discovered NGF in the 1940s, and she later received the Nobel Prize for this work. (For an interesting account of experiments conducted in a closet while hiding from the Nazis during World War II, see Levi-Montalcini's autobiography, *In Praise of Imperfection*.) NGF appears to be an important substance in sustaining neurons, especially after injury. Recent evidence indicates that treatments promoting such growth factors can aid in functional recovery following stroke in animal models, suggesting a possible route for clinical intervention (Wieloch and Nikolich, [2006](#)).

Regional Mechanisms for Recovery of Function

Damage to a discrete region of brain tissue affects more than the cells in that immediate area; an insult can also affect the surrounding tissue and even more distant tissue in the brain. For several reasons, much of what we know about this pattern of damage and recovery of function has come from studies of the motor system. The layout of motor cortex is well understood, changes in motor behavior are relatively easy to observe and measure, and motor cortex damage and recovery can be modeled in nonhuman animals, with whom we share the same basic pattern of motor system organization. In addition, recovery of movement is often a primary target of rehabilitation in people who have suffered strokes.

[Figure 15.21](#) schematically illustrates the regional changes that occur when a discrete area of motor cortex is damaged on one side of the brain (Nudo, [2006](#), [2013](#)). Generally, we can distinguish between three different regions of interest: the region right around the damaged area, sometimes called the penumbra; other regions within that same hemisphere that are related to motor control, such as somatosensory cortex and premotor areas; and analogous regions in the intact opposite hemisphere (i.e., contralesional hemisphere).

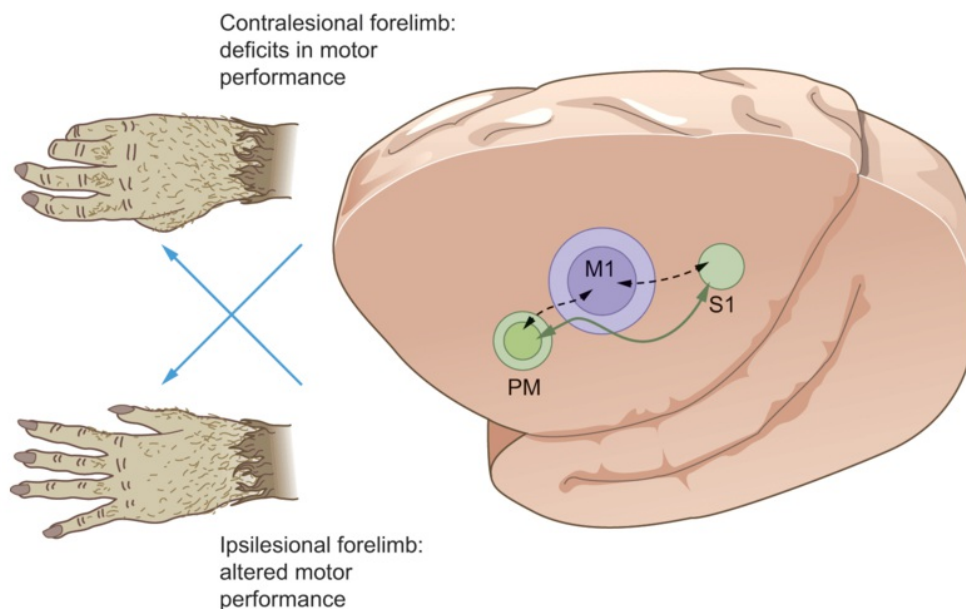


Figure 15.21 Regional effects of damage to a discrete area of primary motor cortex.

The damaged region is shown in darker purple, and the surrounding tissue is shown in lighter purple. Following injury, changes in growth-stimulating and growth-inhibiting proteins occur in the surrounding tissue. Areas S1 (primary somatosensory cortex) and PM (premotor cortex) are also influenced by the lesion. Solid lines represent strengthened pathways, and dashed lines represent lost pathways.

Source: Figure 1 from Nudo, R. J. ([2006](#)). Mechanisms for recovery of motor function following cortical damage. *Current Opinion in Neurobiology*, 16, 638–644. Reprinted by permission of Elsevier.

In cases of relatively small lesions to motor cortex, recovery of function may be supported by the region adjacent to the damaged tissue. In this penumbral region, which is located in a ring around the lesion, changes in gene expression occur. These changes in gene expression result in an increase in proteins that facilitate growth and a decrease in proteins that inhibit growth (Nudo, [2013](#)). The ability of the penumbral region to take over some function of the damaged tissue may be analogous to the ability of somatosensory and motor maps to reorganize in response to changing input, as we discussed in the [preceding section](#).

Damage to a discrete region of primary motor cortex also alters activity in more distant regions of that hemisphere, such as the somatosensory cortex and higher-level motor areas (Nudo, [2013](#)). For example, motor representations in premotor cortex expand (Frost et al., [2003](#)), and pathways between premotor cortex and somatosensory cortex are strengthened as each of them loses connections with the damaged primary motor cortex (see [Figure 15.21](#); Dancause et al., [2005](#)). In this sense, the brain is developing a “work-around” strategy to keep somatosensory and motor areas in communication even though the hub that used to connect them has been damaged.

When the damaged area within primary motor cortex is relatively large, there may not be enough intact tissue in that hemisphere to support recovery of function. In such a case, function may be partly taken over by the parallel region of the opposite hemisphere (Cramer and Crafton, [2006](#)). Numerous studies have shown changes in the contralesional hemisphere, such as dendritic arborization, following unilateral primary motor cortex damage (Jones and Schallert, [1994](#)). Changes in contralesional areas may occur for two different reasons. First, the person may begin to rely more upon the unaffected limb, which is controlled by the contralesional motor area. For example, after left-hemisphere damage that impairs movement of the right arm, a person might begin using the unaffected left arm more, stimulating neural changes in the right hemisphere. Alternatively, the contralesional area may begin to take over control of the impaired limb. For example, after left-hemisphere damage that impairs right-arm movement, the right hemisphere might begin to take control of the right arm.

Our discussion so far has focused on changes in brain organization that occur in sensorimotor regions. Do the same principles apply to recovery of cognitive functions? In the domain of language, controversy currently exists over which neural mechanisms best support language recovery in aphasic patients (for reviews, see Geranmayeh et al., [2014](#); Muñoz-Cespedes et al., [2005](#)). Is recovery due to reorganization within regions of the left hemisphere, or are language functions taken over by the right hemisphere? Evidence can be found to support both viewpoints, and it is difficult to untangle complicating factors such as the specific region of damage, extent of damage, and the aspect of language affected. Language recovery in aphasic patients may also be aided by enhanced engagement of cognitive control systems that reflect increased effort and allocation of attention during linguistic tasks (Geranmayeh et al., [2014](#)).

Researchers are also exploring how brain damage alters functional connectivity, and how improved connectivity may provide a mechanism for recovery of function (Corbetta, [2012](#); Grefkes and Fink, [2014](#); Matthews and Hampshire, [2016](#)). This trend reflects a movement away from strict localization models of the brain, in which each region has a specific function that must be reallocated when the region is damaged in order to promote recovery, and toward models that better appreciate the interactive nature of normal brain functioning. Understanding how closely brain regions are functionally interconnected with one another gives us insight into how damage to a discrete, focal region (such as Broca's area) can have negative consequences for functions that are distributed across brain networks (such as language processing more generally). Furthermore, on a more positive note, the distribution of functions across brain regions, rather than isolation of functions to specific proscribed parts, may make the system more plastic and resilient to injury.

Recovery of Function in Adults

Although research provides evidence of possible brain reorganization after trauma, there are many unanswered questions regarding the degree to which recovery from a traumatic lesion damage is possible. At present, we do not know all of the parameters

that limit the extent of reorganization and recovery, nor do we know exactly how to manipulate conditions to make such reorganization possible. What is clear, however, is that there are multiple factors that influence recovery, and that more recovery is possible in adults than has been traditionally thought. The multiple factors that influence recovery are listed in [Table 15.3](#).

Table 15.3 Factors Likely to Influence Recovery

| |
|---|
| Severity of insult |
| Number of insults |
| Spacing of insults |
| Age at time of insult |
| Premorbid cognitive status |
| Extent to which one function can be taken over by another |
| Overall brain integrity |
| Individual differences in brain structure |
| Motivation |
| Emotional factors |
| Extent and quality of rehabilitation |

Interestingly, research with animal models suggests that the surrounding environment may influence recovery. Earlier, we discussed evidence that environmental enrichment can influence neurogenesis and synaptogenesis in the developing brain. Evidence also indicates that animals housed in enriched environments before or after a brain injury tend to have better outcomes, as shown by both physiological and behavioral measures,

compared to animals housed in impoverished environments (e.g., Johnson, [2013](#); Dhanushkodi et al., [2007](#)). This issue has yet to be fully studied in humans, though the potential clinical applications are intriguing and potentially very important (Janssen et al., [2014](#)).

Another relevant factor is the premorbid cognitive status of the person: those with higher intelligence and education may recover better. As said by a noted scientist more than 70 years ago, “It is not only the kind of head injury that matters but the kind of head” (Symonds, [1937](#)). However, the reason for this better recovery is unclear. On the one hand, more intelligent people may have a greater reserve of capacity, so that suffering a brain insult does not diminish their overall capacity as much as it does in a less intelligent person. On the other hand, it may be that more intelligent people are better at learning or devising strategies to overcome their disabilities.

The distinction between true recovery and compensation is important in understanding possible therapies to promote functional improvement (Zeiler and Krakauer, [2013](#)). Here, true recovery refers to restoring the function or process that was lost. For example, in the motor domain, true recovery would involve being able to regain the same movement patterns that preceded the stroke. In contrast, compensation involves finding another way to achieve the same movement goal, such as using different limbs, muscles, or joint motions. As another example of compensation, a patient who becomes amnesic as a result of temporal lobe damage might carry a notebook or use her phone to take a picture of where she parked her car. This strategy normally would not be used by a neurologically intact person, but is invoked to minimize the loss of a specific skill by relying on functions that are still intact. Generally, studies in both human and animal models indicate that the window of time for true recovery following a brain injury may be limited to the first few months, due to biological factors (e.g., Murphy and Corbett, [2009](#); Zeiler and Krakauer, [2013](#)), while compensatory rehabilitation strategies can be implemented at any time following injury.

Although some recovery of function can happen spontaneously even without explicit training (Cramer, [2008](#)), researchers and clinicians are interested in understanding

whether specific training programs can enhance recovery. In studies of motor skills following stroke in animal models, training on specific motor tasks after the stroke appears to promote recovery (e.g., Biernaskie et al., [2004](#)). Likewise, a recent review supported the use of physical therapy to regain motor function after strokes in humans (Veerbeek et al., [2014](#)). However, it is less clear whether motor training can confer general benefits beyond the task that was specifically trained.

While studies of post-stroke training to promote recovery have often focused on motor domains for valid reasons, more research is needed to understand how principles extracted from motor training can be applied to cognitive domains such as language and memory. One similarity across domains is an emphasis on repeated use of the affected function as a tool for recovery in both acute and long-term time frames. For example, some beneficial therapies for aphasia emphasize expecting the patient to use spoken language, however difficult it may be, rather than relying upon other means of communicating such as writing or gesturing; other therapies promote spoken conversation in social groups (e.g., Allen et al., [2012](#)). Some research has found that such aphasia therapies can affect neural measures, such as functional connectivity, alongside improvements in function (e.g., Marcotte et al., [2013](#); see Geranmayeh et al., [2014](#), for review).

In addition to training that targets the behavioral or functional level – such as speech therapy for aphasia or physical therapy for motor skills – other possible avenues for recovery target the brain more directly through stimulation methods. For example, excitatory TMS or tDCS stimulation of motor cortex in a hemisphere damaged by a unilateral stroke appears to contribute to some motor improvements (Dimyan and Cohen, [2011](#)). Inhibitory stimulation of the opposite hemisphere also may lead to improvements, probably by decreasing competition from the intact hemisphere. Transcranial stimulation of left-hemisphere language areas with either TMS or tDCS may also have benefits for language recovery in aphasia (e.g., Baker et al., [2010](#); de Aguiar et al., [2015](#); Hamilton et al., [2011](#)). These methods are generally considered as possible supplements to functional training, rather than substitutes, and numerous

questions remain regarding their optimal timing, duration, and intensity for therapeutic purposes.

Recovery of Function in Children

If you had to choose between brain damage early in life and brain damage later in life, which would you choose? One factor you might want to consider is the extent to which the plasticity of the developing brain aids in recovery of function. Indeed, probably the most dramatic difference between adults and children after brain insult is the seemingly miraculous recovery that children appear to make. For decades, scientists have thought that the earlier in life damage is sustained, the better the recovery. This maxim became known as the [Kennard principle](#), named after the scientist who first proposed such an effect, Margaret Kennard (Kennard, [1936](#), [1942](#); see Dennis, [2010](#)).

Some support for the Kennard principle comes from the study of language in brain-damaged children and adults. Lesions that would leave adults with little or no capacity for language do not have such dire consequences for children. For example, children with left-hemisphere brain damage do not typically exhibit aphasia. In one study, researchers systematically assessed a number of linguistic functions in both children and adults with unilateral brain damage (Bates et al., [2001](#)). The children in the study had congenital brain damage, whereas the adults had acquired brain damage during adulthood. Across various measures, children with brain damage appeared to perform more similarly to their peers, regardless of the hemisphere of damage; in contrast, adults with left-hemisphere damage were especially impaired relative to age-matched controls. However, this should not be taken to mean that there are no consequences of early brain damage on language functioning. Rather, studies have indeed found deficits in phonology, syntax, and linguistic semantics among children with early unilateral brain damage, even if those consequences are less pronounced than the full-blown aphasia seen in adult patients (e.g., Avila et al., [2010](#)).

Indeed, the picture is not completely rosy for children with brain damage. For example, children with damage to the right hemisphere of the brain develop difficulties

in spatial cognition that seem analogous to those of right-hemisphere-damaged adults (Stiles et al., [2005](#)). As illustrated in [Figure 15.22](#), drawings by right-hemisphere-damaged children show the same patterns of disorganization as those of adults with similar areas of brain damage. In addition, some research indicates that brain damage sustained either within the first year of life or after the age of 6 produces worse outcomes on a range of neuropsychological measures compared to damage between the ages of 1 and 6 years (Allman and Scott, [2013](#)). This finding suggests that the relationship between age of damage and cognitive outcome does not necessarily follow a linear “earlier is better” pattern.

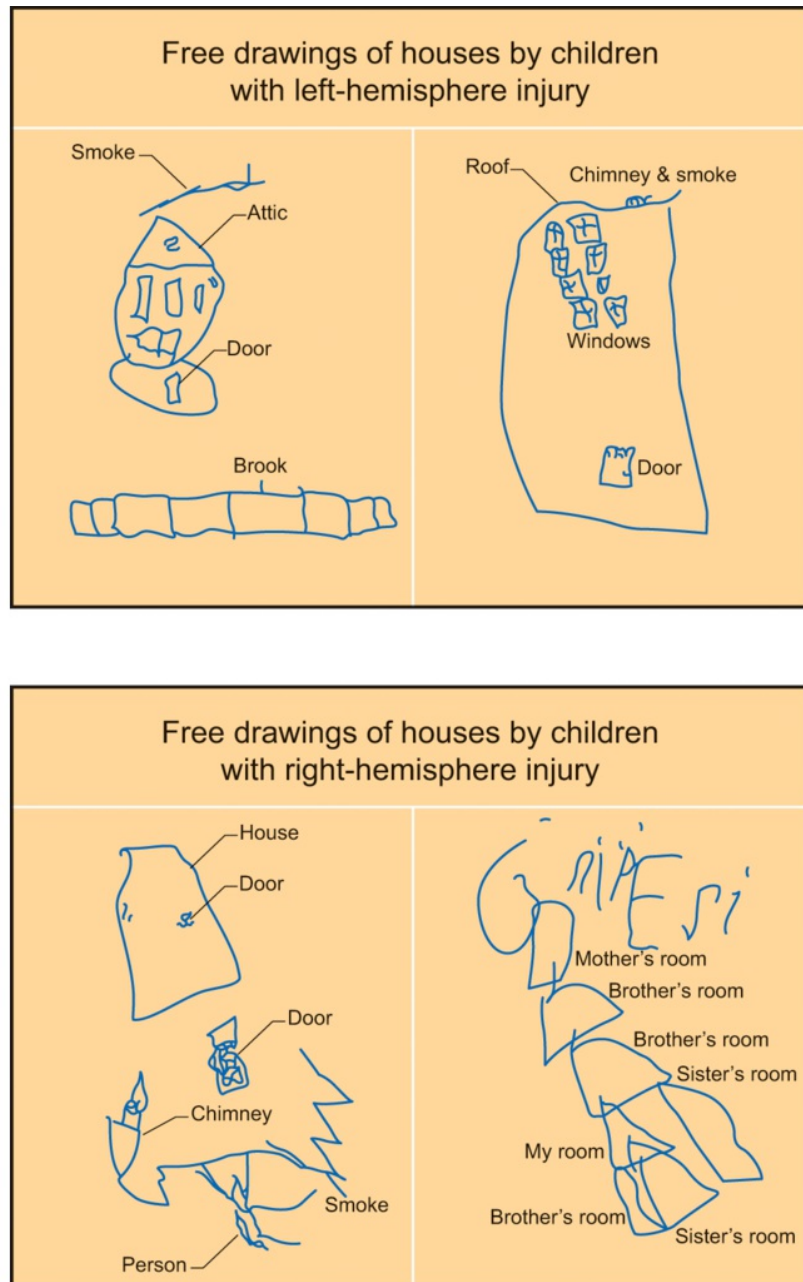


Figure 15.22 Drawings made by children with left- and right-hemisphere brain damage early in life.

The deficits in the right-hemisphere-damaged children's drawings are similar to the deficits seen in adults with right-hemisphere damage.

Source: Figure from Stiles-Davis, J. et al. (1988). Drawing ability in four young children with congenital unilateral brain lesions. *Neuropsychologia*, 26, p. 365.

Reprinted by permission from Elsevier.

Other evidence points to the importance of considering the whole time course of development when assessing the impact of childhood brain damage. In other words, researchers must consider not only the age at which a child sustains a lesion, but also the age at which the child is being assessed and the amount of time that has passed since the injury (Anderson et al., [2011](#)). Children may appear to be relatively resilient early in development, with deficits emerging only later as the child is expected to demonstrate more and more complex skills. For example, one study found that children with congenital brain damage showed declines in IQ after the age of 7, as they failed to keep up with their peers in cognitive development (Levine et al., [2005](#)). Other evidence suggests that early-occurring brain damage may actually produce worse long-term consequences for IQ than later-occurring brain damage, in contrast to the Kennard principle (Duval et al., [2008](#)). Whereas the consequences of a brain injury acquired in adulthood are usually soon obvious, for a childhood-acquired injury, it may be years before the full consequences become manifest.

One possible explanation of later-emerging deficits is the [crowding hypothesis](#) (e.g., Teuber and Rudel, [1962](#)). According to this idea, the intact areas of the child's brain are now expected to carry out the functions that they would normally implement, as well as the functions that the damaged area would normally have implemented. In other words, too many functions are crowded into the intact brain tissue. This becomes more and more evident with development as the child is expected to develop more complex skills, and may account for why higher-order skills such as attention and executive functioning are affected following early brain damage (O'Keeffe et al., [2014](#)). If we only needed three-quarters of a brain to function optimally, evolution probably would have given us a three-quarters-sized brain! Thus, it should not be surprising that childhood brain damage does have a cost, even given the remarkable plasticity of the developmental period.

Finally, we cannot think of "childhood" as simply one category of time compared to "adulthood." Damage to the brain at different points in childhood may have different

consequences. For example, research on rats has shown that damage to the brain produces the worst functional outcomes when the damage occurs just after neurogenesis is complete, whereas damage occurring slightly later, during the period of synaptogenesis, is associated with better outcomes (Kolb and Gibb, [2001](#)). Some evidence suggests that the brain is especially vulnerable in the perinatal period, with worse outcomes when damage occurs in this period compared to the early postnatal years (Anderson et al., [2011](#)). Furthermore, throughout childhood, the effect of brain damage on a particular skill may depend on whether that skill is already established or still developing; evidence generally suggests better recovery for already established skills rather than skills that are in the midst of being developed at the time of injury. Generally speaking, because the brain is in a different state at different points during early development, the consequences of a brain injury will depend upon its timing.

In Focus: Can Deprivation in One Sensory Modality Promote Extraordinary Abilities in Another?

In this chapter we have discussed how plasticity allows the brain to reorganize in response to injury or atypical environments (e.g., sensory deprivation), in some cases allowing the person to attain or reacquire a normal complement of abilities. But can reorganization actually enhance the brain's processing capacity beyond normal levels? You may have heard "common wisdom" that blind people can hear better, or deaf people can see better, compared to everyone else. Here we discuss the empirical evidence pertaining to this question.

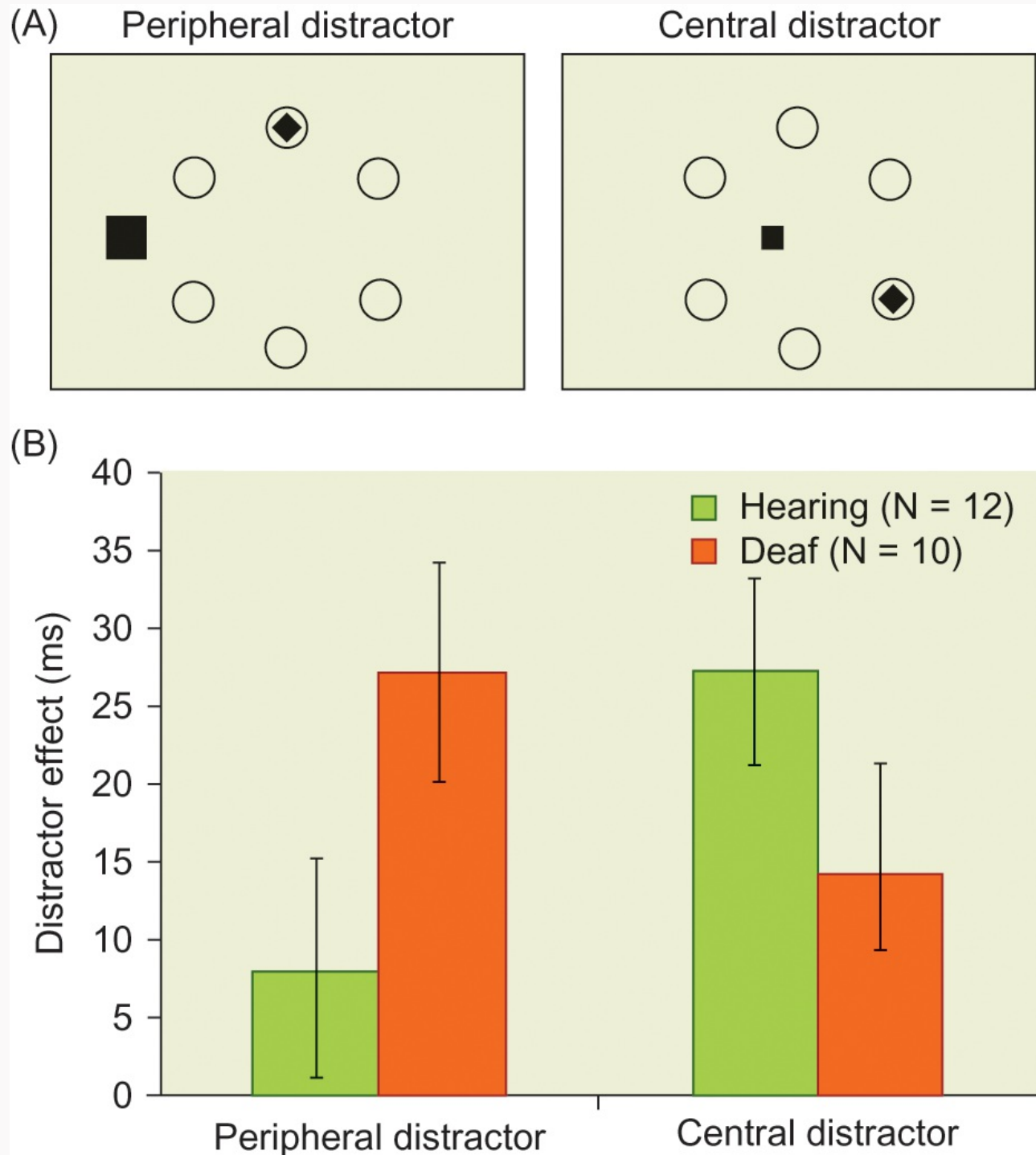
First the bad news: deprivation of a particular sensory input from birth does not seem to enhance basic sensitivity in the remaining sensory modalities. For example, auditory deprivation due to deafness does not alter the threshold at which light can be detected or the ability to distinguish different levels of visual contrast (Bavelier et al., [2006](#)). These findings imply that little, if any, reorganization occurs in the sense organs and initial processing steps in the intact

sense. Yet, the possibility remains that perception and cognition may be enhanced in more subtle ways. Here we consider examples from the study of people who have lost either hearing or vision.

Current evidence suggests that people who are deaf are especially sensitive to visual motion. For example, one study found altered motion-detection thresholds in people who were deaf either from birth or soon after birth (Shiell et al., [2014](#)). Participants viewed two sinusoidal grating patterns, one of which was moving very slightly, and they had to indicate which one was moving. Deaf participants were able to reliably detect smaller amounts of movement than hearing participants. Converging evidence of improved visual motion detection comes from studies of congenitally deaf cats, who showed enhanced motion detection (detecting which of two arrays of dots is moving) without any enhancement in basic visual acuity (distinguishing which of two lines is longer; Lomber et al., [2010](#)). This enhanced visual motion detection appears to depend on reorganization of a dorsal portion of auditory cortex, because temporarily inactivating this region eliminated the performance advantage in detecting visual motion in deaf cats (Lomber et al., [2010](#)).

Other evidence indicates that people who are deaf are differentially responsive to visual information in the periphery, as opposed to central vision (Dye and Bavalier, [2010](#)). Intuitively, this makes sense: normally, auditory cues in the periphery help us to reorient our gaze to fixate on a peripheral stimulus. For example, if you hear something near your left shoulder, you would probably shift your gaze toward the left, bringing the object into central vision. Because deaf people receive no auditory cues from the periphery, vision itself must become more sensitive to events in peripheral regions of space. In one study, participants had to respond to a visual target while a distractor appeared either in the center or the periphery of the display (see [Box Figure 15.1](#)). Deaf people were more influenced by the distractor when it appeared in the periphery,

whereas people with normal hearing were more influenced by the distractor when it appeared in the center (Proksch and Bavelier, 2002).



BOX Figure 15.1 Attention to peripheral versus central visual information in deaf versus hearing individuals.

When making a decision about the symbol in the circle, deaf people are more influenced by a distracting shape in the periphery, whereas hearing people are more influenced by a distracting shape in the center.

Source: Bavelier, D. et al. (2006). Do deaf individuals see better? Trends in Cognitive Sciences, 10, 512–518. Reprinted by permission of Elsevier.

Likewise, congenitally deaf cats also show enhancements in detecting visual stimuli in the periphery (Lomber et al., 2010). In a task that required detecting a visual target at various distances from the center of a display, deaf and hearing cats did not differ for central targets, but deaf cats had a performance advantage for peripheral targets. Inactivating the primary auditory cortex eliminated this advantage, implying a repurposing of auditory cortex for peripheral vision. Interestingly, different subregions of auditory cortex appeared crucial for enhanced visual motion versus peripheral visual target detection in the deaf cats. This latter finding suggests that the auditory cortex reorganized into different functional units to support different aspects of compensatory vision in the deaf cats.

Deaf people may also rely differently on touch information, as well as visual information, compared to hearing people. Evidence from human neuroimaging studies indicates that portions of auditory cortex are repurposed for both tactile and visual sensations in deaf people, as these regions are activated more to touch and visual sensations in deaf than hearing people (Karns et al., 2012). Interestingly, the same study found that deaf people were also more susceptible than hearing people to a cross-modal illusion in which two touches to the face combined with a single flash of light produce an illusory perception of two light flashes. Activity in auditory cortex in response to bimodal (touch plus visual) information predicted the strength of this illusion in deaf people, suggesting that it might be the combined reorganization of this cortical region for both vision and touch that enhances the illusory cross-modal perception. This example

illustrates that reorganization can sometimes have unexpected side effects on perception!

These studies focused on visual perception in those who have lost hearing, but other studies have focused on perception and cognition in those who have lost sight. One interesting line of research has examined the verbal memory abilities of blind people. Many cultural traditions feature blind storytellers, who pass on narrative histories reliably by word-of-mouth. It is logical that blind people might need to rely on verbal memory more than sighted people, because blind people are unable to rely on visual information.

Indeed, several studies have reported superior verbal memory in the blind, in addition to enhancements in aspects of auditory and tactile processing (Kupers and Ptito, [2014](#)). Neuroimaging studies have found that verbal tasks activate primary visual cortex (area V1) in congenitally blind people but not in sighted controls (Amedi et al., [2003](#); Röder et al., [2002](#)). Further, disruption of visual cortex activity with TMS leads to semantic errors in a verbal task in blind but not sighted people (Amedi et al., [2004](#)). These studies imply that “visual” cortex has been reorganized to support verbal functions. Linking these findings together, in one study the degree of activity in V1 predicted verbal memory performance among blind (but not sighted) people (Amedi et al., [2003](#)). Other neuroimaging evidence indicates that among congenitally blind people compared to sighted people, occipital cortex shows greater functional connectivity with areas in the frontal lobe thought to be important for language (Bedny et al., [2011](#)).

It may seem amazing that an area that is normally so clearly dedicated to representing visual features can be reorganized to represent a very different kind of information. It is easier to think of how visual cortex could be reorganized to support Braille reading (see earlier discussion in this chapter), because Braille letters have a kind of spatial organization that could map onto the spatial layout of area V1. Because researchers do not have a good understanding of how verbal information is organized even in the normal brain, it is still unclear how such

information could be represented in V1 in the brain of someone who is blind. Nevertheless, existing studies provide at least preliminary evidence that reorganization of V1 to serve verbal functions may contribute to enhanced verbal memory skills in people who are blind.

Changes in the Brain With Aging

Changes in brain functioning occur not only during childhood and as a result of brain damage, but also as a result of the aging process. These changes become more noticeable as a person approaches the later adult years. In this last section, we consider some of the cognitive and neural changes that accompany old age. Here, we focus on change associated with healthy aging. The topic of dementia, such as seen in Parkinson's and Alzheimer's disease, is addressed in [Chapter 16](#).

Cognitive Changes With Aging

Broadly speaking, there are several different ways to view the changes in mental function that accompany age. We can focus on the nature of decline with aging, considering whether decline is general (i.e., everything gets worse with age) or specific to certain abilities (i.e., some functions get worse at a faster rate than others). In addition, we can also consider how the cognitive strategy employed by an older person differs from that of the young adult mind, and whether there are some ways in which older people actually may perform better than younger people.

Most studies of aging have taken a decline-related approach. One viewpoint argues that there is a general decline across all abilities with age. This decline may represent a general reduction in mental resources or a general slowing in the speed of processing (Salthouse, [2000](#)). Evidence for this theory comes from comparing the performance of young adults and older adults (usually early retirement age or older) across a variety of tasks. Generally, older people perform worse than younger people on a wide range of tasks.

Yet, some aspects of cognitive processing are more compromised in older persons than other aspects of processing. For example, cognitive declines in aging appear to be most pronounced for explicit memory recall tasks (e.g., memorizing and recalling lists of words) and for tasks of executive functioning. In contrast, autobiographical memory, vocabulary, and implicit memory processes seem relatively intact (Hedden and Gabrieli, 2004). Age-related declines are most pronounced on novel problem-solving tasks, sometimes referred to as tasks of “fluid intelligence,” whereas performance does not decline on tasks that depend on accumulated knowledge, sometimes referred to as tasks of “crystallized intelligence” (see Figure 15.23; Salthouse, 2012). Such evidence fits with our commonsense notions that our elders seem wise and knowledgeable even though they may not be as quick-thinking as their younger counterparts!

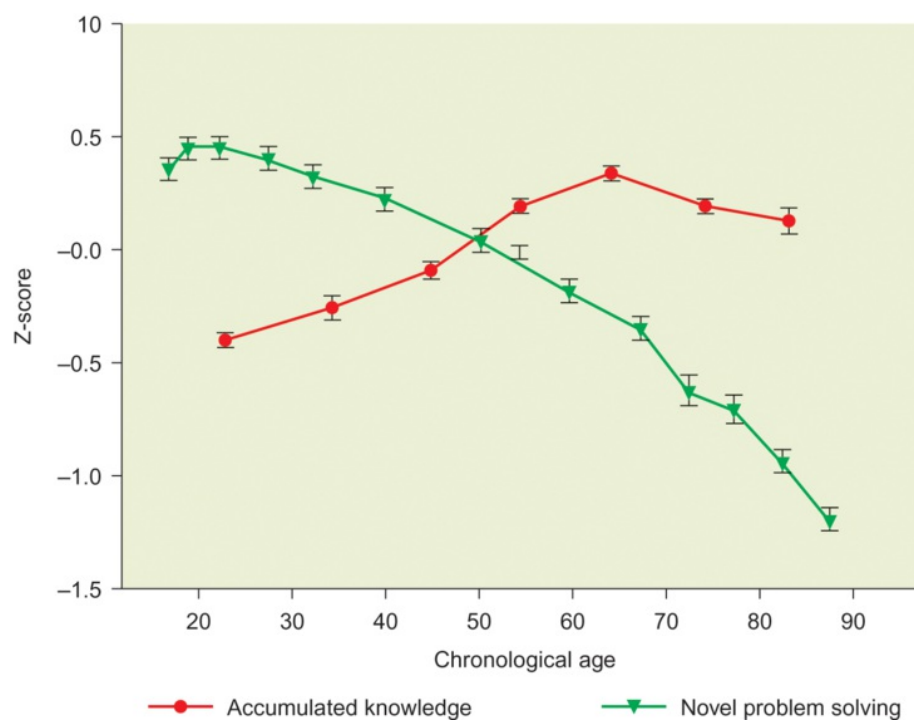


Figure 15.23 Age-related changes in fluid and crystallized intelligence.

Generally, aging has a greater negative impact on measures of novel problem solving (sometimes referred to as fluid intelligence), whereas tasks that tap accumulated knowledge (sometimes referred to as crystallized intelligence) are less affected by aging.

(from Salthouse, 2012)

Researchers must also consider whether cognitive strategies shift with age; they cannot simply test whether older people perform worse and at what rate performance declines. In some cases, older people may perform as well as young adults, but they may use a different strategy to complete the task. For example, older adults might rely more upon stored knowledge – the accumulated wisdom from years of life – rather than upon processing speed to perform a particular problem-solving task. In such cases, we might not be able to detect age-related processing changes on the basis of performance measures alone. In other cases, the way a task is framed can influence the degree to which an age-related effect is seen. For example, one study found that instructing participants to focus on the meaning of a memory task (rather than simply letting participants use whatever strategy they wanted) reduced the age discrepancy in performance and produced patterns of brain activity that were more similar between age groups (Logan et al., [2002](#)). Such findings indicate that young and older people may at times tend to use different cognitive strategies for the same task.

Finally, aging may actually be associated with improved performance on some tasks. Studies suggest at least one domain in which aged people outperform young people: emotion regulation (for reviews, see Mather, [2012](#); Reed and Carstensen, [2012](#)). Whereas older people are generally impaired on tasks of working memory and attention compared to younger people, they show no impairment when the task involves emotional information (Mikels et al., [2005](#); Samanez-Larkin et al., [2009](#)). Older people appear to be better able to cope with emotionally distressing situations; their negative moods tend not to persist as long as those of younger people and their positive moods persist longer (Carstensen et al., [2000](#)). Older people also tend to show positive attentional biases, shifting attention toward positive information and away from negative information in standard lab tasks (Mather et al., [2004](#)). Although we may question whether it is always good to see the world through rose-colored glasses, it certainly can make the later years of life more enjoyable!

Neural Changes With Aging

In recent years, an explosion of studies has focused on changes in the brain with aging (e.g., Grady, [2012](#); Reuter-Lorenz and Park, [2014](#)). Brain imaging studies indicate that some age-related changes in brain structure and activity are region-specific. For example, volume declines measured by structural imaging are more prominent in the frontal lobes and less pronounced in primary sensory areas (see [Figure 15.24](#); Raz et al., [2005](#), [2010](#)). Reduced activity is also seen in medial temporal regions, associated with memory processing, and visual regions across a wide variety of tasks (Grady, [2008](#)).

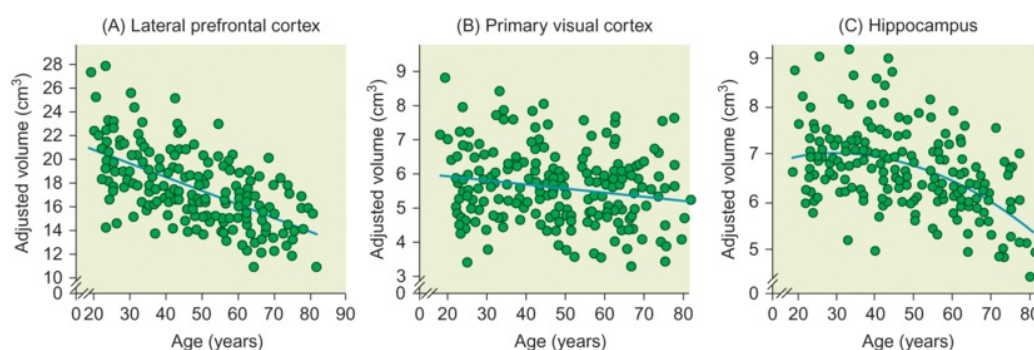


Figure 15.24 Changes in brain volume with age for three different brain regions.

From Hedden and Gabrieli, [2004](#).

Interestingly, the regions of the brain that begin to degenerate soonest during the aging process are similar to those that are latest to mature during the early years of development. In this way, aging may be somewhat like developing in reverse (Raz, [2001](#)). For example, one study examined structural images of the brain in a sample of nearly 500 participants ranging from 8 to 85 years of age (Douaud et al., [2014](#)). Using statistical methods, the researchers were able to identify brain areas that show a relatively linear path of development (gray matter declining with age) as well as another set of areas that showed a curvilinear trajectory, such that volumes were smallest at both the beginning and end of the lifespan and highest in the middle decades (see [Figure 15.25](#)). Evidence of brain regions exhibiting this curvilinear pattern, which include lateral frontal, intraparietal, and medial temporal cortices, support a “last in, first out” model of regional brain volume change over the lifespan.

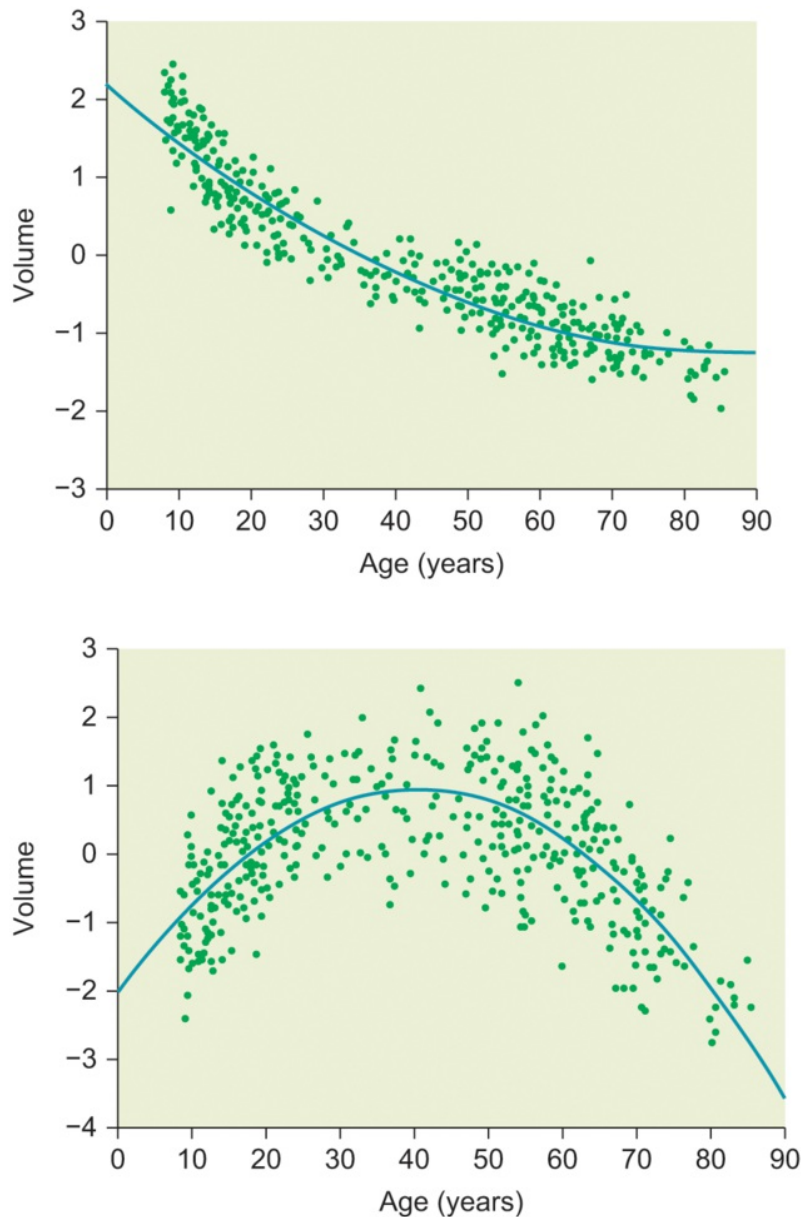


Figure 15.25 Two different trajectories of brain volume over the lifespan.

Across the lifespan, some brain regions show linear decreases in volume (top panel) whereas other regions show a curvilinear pattern in which volumes are highest in midlife and lower in both early and later years of life.

(from Douaud et al., [2014](#))

These neural changes appear to have behavioral consequences. Over the years, studies have confirmed that cognitive functions supported by frontal regions and temporal regions are particularly compromised with age (Hedden and Gabrieli, [2004](#); Yuan and Raz, [2014](#)). For example, older adults exhibit deficits on a battery of tests

sensitive to frontal lobe damage, such as the self-ordered pointing task, the Wisconsin Card Sorting Test, verbal and design fluency, and the Stroop task. They also show clear declines in memory tasks that rely on frontal regions. These include working memory tasks; “meta-memory” tasks, such as knowing the temporal order in which information was received; prospective memory tasks, which require remembering to carry out a function at a future time; and [source memory](#), which is the ability to remember the specific circumstances or context in which particular information was learned (e.g., knowing that you learned that the earth orbits the sun in your third-grade class taught by Ms. Frost). As we learned in [Chapter 9](#), the temporal lobes, and particularly the hippocampus, are critically important for creating new long-term declarative memories, memories that allow information to be used flexibly and in a variety of contexts. By the sixth and seventh decades of life, healthy older adults begin to perform more poorly than younger adults on direct tests of declarative memory.

Nevertheless, there are many interesting cases in which older adults show increased brain activation compared to younger adults. These increases are often prominent in exactly the regions that are affected by aging, such as prefrontal cortex. How are we to understand this seemingly counterintuitive finding? One possibility is that these regions are neurally inefficient – they must work doubly hard because they are working poorly, leading to increased activation (e.g., Cabeza et al., [2000](#)). However, an intriguing alternative explanation is that these regions become more active in a compensatory manner to overcome declines in functioning in other brain regions (Park and Reuter-Lorenz, [2009](#); Reuter-Lorenz and Park, [2014](#)). Supporting this idea, older individuals who perform better on working memory tasks seem to show the greatest degree of engagement of prefrontal regions (Rypma et al., [2007](#)).

Aging affects not only the integrity of specific brain regions, but also the global pattern of activation across the brain. One prominent theory is that [dedifferentiation](#) causes the localization of function to become less defined with age (Li and Lindenberger, [1999](#)). For example, older adults show less specificity in activity in the fusiform face area, parahippocampal place area, and lateral occipital area in response

to stimuli that typically activate these regions (faces, houses, and letters/words, respectively) (Park et al., [2004](#), [2012](#)). Patterns of functional connections across the brain also become less differentiated with age. For example, among younger adults, there is an inverse correlation between activity in the default mode network and activity in a network of regions associated with externally directed attention, such that greater activity in one of these networks is associated with lesser activity in the other one. In older adults, this inverse correlation becomes weaker, suggesting less pronounced differentiation between the networks (Spreng et al., [2016](#)).

These findings, however, do not mean that the elderly brain becomes one large, undifferentiated mush. In fact, one elegant series of studies suggests that some additional activations may be due to increasing task demand. Unlike younger adults, who activate left prefrontal regions during verbal working memory tasks and right prefrontal regions during spatial working memory tasks, elderly adults tend to exhibit bilateral activation for both verbal and spatial working memory (Reuter-Lorenz et al., [2001](#); see also Cabeza, [2002](#); Cabeza et al., [2004](#)). One possibility is that the bilateral pattern of performance indicates that the elderly adults need to engage both hemispheres because of reduced abilities in each hemisphere. Supporting this view, older adults who performed better on a memory encoding task had more bilateral frontal activation than those who performed worse (Rosen et al., [2002](#)). These results imply that bilateral patterns of activation in the elderly reflect a compensatory strategy of recruiting additional brain regions to support performance, a strategy that can also be helpful for younger participants when they are experiencing highly demanding task conditions (Höller-Wallscheid et al., [2017](#)).

Another possible reason why the pattern of activation might change in the elderly is that there is a greater disconnection between brain regions as a result of a loss of myelin. Studies of white-matter loss in aging have shown generalized declines that are most pronounced in the frontal lobes and the anterior corpus callosum (Bennett and Madden, [2014](#)). This greater disconnection could explain in part why executive control by frontal regions is compromised by aging. Older people would be less able to exert

top-down attentional control over other parts of the brain; for example, they might be unable to rev up activation of brain regions involved in processing task-relevant information (such as identifying the ink color in the Stroop task) while dampening down activation of brain regions involved in processing task-irrelevant information (such as the irrelevant word information in the Stroop task). In fact, measures of white-matter integrity are found to be better predictors of cognitive performance in the elderly than the degree of gray-matter loss. In particular, one study found that white-matter integrity in the frontal lobe predicted executive function, whereas that in the temporal and parietal lobe predicted episodic memory, the ability to remember certain events or episodes (Ziegler et al., [2010](#)).

Slowing the Effects of Aging

Just as Ponce de León went searching for the fountain of youth, scientists have embarked on a voyage to determine what can help keep the elderly mentally young. Two factors have emerged as helping to slow the effects of aging: aerobic exercise and remaining intellectually active. Our knowledge of the importance of these factors was initially gleaned from animal research and then shown to be equally important for people. Each factor helps to sustain the brain by a distinct mechanism. Aerobic exercise produces a greater proliferation of blood vessels to the brain, resulting in enhanced oxygen supply. In addition, as we discussed earlier, a mentally stimulating environment produces an elaboration of dendritic trees, allowing more numerous and varied synaptic connections. We discuss each in turn.

Increasing evidence now supports the conclusion that aerobic exercise has beneficial effects on cognitive tasks during aging (for reviews, see Bherer et al., [2013](#); Hillman et al., [2008](#); Kramer and Erickson, [2007](#)). Research with animals indicates that exercising leads to greater proliferation of the blood supply to the brain. Oxygen insufficiency, whether caused by pulmonary disease, cigarette smoking, or being on a high mountaintop, can lead to deterioration in neuropsychological functioning. It is not surprising, therefore, that people who engage in aerobic exercise have better

neurocognitive functioning than their nonexercising peers (e.g., Aichberger et al., [2010](#); Barnes et al., [2003](#); Sofi et al., [2011](#)). One limitation of such studies, however, is that these people might be particularly blessed physical specimens, which is why they retain their mental faculties and can continue to exercise into old age. In other words, the correlation between physical health and cognitive functioning does not necessarily tell us about the causal role of exercise in mental functioning.

To examine whether exercise can aid the average person, one group of researchers (including the first author of this textbook) selected people aged 60–75 who did not exercise, being “couch potatoes” who preferred to watch television or read (Kramer et al., [1999](#)). These individuals were enrolled in a six-month program of either light aerobic exercise (e.g., 30 minutes of brisk walking three times a week) or a toning and stretching program that involved no aerobic exercise (e.g., 30 minutes of stretching exercises three times a week). At the end of the six-month period, the aerobic exercise group showed fewer age-related deficits on attentional and memory functions that rely on prefrontal regions of the brain, compared to the stretching and toning group. This study demonstrated that the beneficial effect of exercise on cognition was specific to aerobic exercise, and that even relatively low levels of such exercise can have significant effects (see meta-analysis of similar studies by Karr et al., [2014](#)).

One mechanism by which exercise may impact cognition in the aged brain is through neurogenesis, the formation of new neurons. For example, one study housed both young and old mice either with or without access to a running wheel (van Praag et al., [2005](#)). The researchers later examined cognitive functioning, measured by performance in a maze task, and neurogenesis in the hippocampus. While older mice generally performed more poorly than younger mice on the maze task, this age-related deficit was reduced by access to a running wheel. Moreover, older mice housed with the running wheel showed increased levels of neurogenesis compared to older mice without access to the wheel. Although neurogenesis cannot be measured directly in living humans, one study in people reported that aerobic exercise led to an increase in hippocampal size as well as improvement in performance on a spatial learning task (Erickson et al., [2011](#)).

A stimulating environment may also stave off some of the more negative effects of aging (for reviews, see Hertzog et al., [2009](#); Lindenberger, [2014](#)). Enriched environments enhance neurogenesis among older mice (Kempermann et al., [2002](#)), suggesting a similar mechanism by which both exercise and cognitive enrichment could impact cognitive functioning in older age. A longitudinal study of about 4,000 older adults in Chicago found that participants' self-reported participation in a mentally stimulating activity, such as reading, predicted a slower rate of cognitive decline in the future (Wilson et al., [2003](#)).

Likewise, cognitive training programs may be effective interventions for slowing age-related decline. For example, in one study both younger and older adults practiced specific tasks of perceptual speed, working memory, and episodic memory for an hour daily for 100 days (Schmiedek et al., [2010](#)). The participants showed improved performance not only on the specific tasks on which they trained, but also on other measures of general cognitive function, such as reasoning. In general, then, while age-related decline is to some degree inevitable, active choices about exercise and intellectual stimulation can help you to stay mentally sharp far into your older years.

Summary

Development of the Brain

- Nerve cells proliferate during gestation, whereas glia proliferate after birth.
- Physiological changes during childhood include an overproduction and then pruning of synaptic connections, increased myelination, and more organized and long-range patterns of functional connectivity.
- Developmental changes in brain structure and function are accompanied by changes in the cognitive skills of the child that occur in an orderly fashion, such as crawling before walking.

- The environment can have profound effects on the developing brain, especially during sensitive periods, during which information from the environment has a lifelong effect on the brain's organization and capacity.

Developmental Disorders

- Intellectual disability is characterized by a lack of ability across a wide range of cognitive domains. It can be caused by various factors, including infections, genetic disorders, and toxins such as alcohol.
- Dyslexia is an inability to read despite adequate intelligence in other domains and schooling in the reading process. It is associated with atypical anatomy and function of language regions of the left hemisphere, and possibly poor integration of information between brain regions.
- Autism is characterized by a profound lack of desire to interact emotionally or socially with other people. Early behavioral signs of autism are evident within the first year of life, and brain development appears to follow a different trajectory than typical development in both cortical thickness and white-matter development.
- Children with attention-deficit/hyperactivity disorder have difficulty concentrating, are physically restless, cannot focus their attention on a task, and tend to be impulsive. Dysregulation of the dopaminergic system is implicated in this disorder, as well as prefrontal regions of the brain, the basal ganglia, and possibly the anterior cingulate.
- Children with learning disabilities rarely outgrow them, although the condition may manifest itself differently in adulthood. For example, whereas a hyperactive child might have trouble sitting in a chair in class, a hyperactive adult might not be able to "sit with" a problem.

Brain Plasticity and Recovery of Function

- The adult brain can be reorganized in response to changes in sensory input and experience, although there are limits to the capacity for reorganization.
- A vast physiological response occurs to brain injury, including the degeneration and death of nerve cells, the cleaning up of debris by glia, swelling (known as edema), and eventually the formation of a scar. Lesions may disrupt other aspects of brain functioning, such as metabolic rate, neurotransmitter release, and oxygen consumption.
- At the cellular level, compensatory mechanisms for neural injury include an increased sensitivity to neurotransmitters and the formation of new connections by rerouting and sprouting.
- Injury to a specific region of the brain can affect activity in neighboring regions, as well as parallel regions in the opposite hemisphere. These regional activity changes may aid in compensating for the loss of the damaged tissue.
- Factors influencing recovery of function in adults include the premorbid status of the individual, repetitive training, and the use of compensatory or alternative strategies.
- Although the Kennard principle posited that recovery of function in children is superior to that in adults, recent studies suggest that the deficits observed after brain damage in children may emerge or recede depending on the time since the lesion and the developmental stage at which a function is examined.

Changes in the Brain with Aging

- Some theories posit a general slowing or overall reduction in capacity with age, but evidence from cognitive neuroscience suggests that the changes with age are more specific.
- Brain regions most susceptible to the effects of aging include the frontal and

temporal regions.

- With aging, the brain appears to exhibit less localization of function, which may occur because older individuals attempt to recruit more brain areas to compensate for lost function.
- Engaging in aerobic exercise and being in a stimulating environment appear to stave off the effects of aging, possibly because both processes aid in the formation of new neurons in the adult brain.

Chapter 16

Generalized Cognitive Disorders



[Closed Head Injury](#)

[Etiology](#)

[Neuropsychological Consequences](#)

[Intervention](#)

[In Focus: Closed Head Injury and Sports](#)

[Dementing Diseases](#)

[Cortical Dementias](#)

[Alzheimer's Disease](#)

[Frontotemporal Dementia](#)

[Subcortical Dementias](#)

[Parkinson's Disease](#)

[Huntington's Disease](#)

[Mixed-Variety Dementias](#)

[Multiple Sclerosis](#)

[Epilepsy](#)

[Disorders of Conscious Awareness](#)

[Summary](#)

A strong and determined woman, L.F. immigrated to the United States from Italy in the early 1900s when she was in her twenties. She came alone, without family or friends – a journey that few women dared to make at that time, especially under such circumstances. After arriving in the United States, she bucked tradition, setting out on her own and not marrying immediately, even though she was already considered an “old maid.” Eventually she met a fellow Italian immigrant who suited her taste, and they married.

Their life together started out well. Her husband was a successful small businessman, and along came four children, the last two of whom were born when L.F. was in her forties. However, when the financial markets collapsed at the beginning of the Great Depression, the debt her husband had incurred building multifamily dwellings caused him to lose everything. Determined that all her children would nonetheless get a college education (which they all eventually did), L.F. worked 10- to 14-hour days for years as a seamstress, doing intricate embroidery and beadwork for numerous garment makers in New York City. Despite the family’s dire poverty, she instilled in her children a strong work ethic, a love of learning, and a sense of pride.

When she was in her early eighties, L.F. and her husband were forced to leave the apartment building and neighborhood in which they had lived for the past 40 years. The property had been sold to a new owner and was to be converted into a bank. So they went to live with their second-eldest daughter’s family. L.F.’s memory had been deteriorating for some time, and moving into a new home was exceedingly difficult for her. Beset by forgetfulness and disorientation, this once vibrant, resourceful, and proud woman, who had traveled the streets of New York City with ease, now had difficulty navigating from one room to the next. She was disoriented in both space and time, often confusing whether it was morning or night. L.F. would wander aimlessly around the house, especially at night, searching for an item whose location she couldn’t

remember. On rare occasions she would even have a brief bout of paranoia. Once, for example, while her daughter was adjusting her seat belt for a trip to the grocery store, L.F. muttered in Italian that her ungrateful daughter was taking her to be killed.

The strain on L.F.'s daughter's family was great. The house was small, and L.F.'s wanderings, especially at night, disrupted everyone in the house. During these jaunts, she would move various items all over the house, open and close cabinets, turn lights on and off, and sometimes leave her dentures in bizarre locations. Because she found the world so confusing, it was important to keep the house as orderly as possible. This degree of order was sometimes difficult for her grandchildren to maintain. They were still in grade school and junior high, so just keeping their own rooms clean was a challenge! And L.F.'s grandchildren found it difficult to have their friends come over to play because L.F.'s paranoia might cause her to follow their friends around the house to ensure that they weren't stealing anything.

About nine months later, L.F. and her husband moved to the other half of the duplex in which their eldest daughter and family lived. These new living arrangements were much more suitable for the couple. L.F. could wander without disturbing others and the house could be organized specifically to accommodate her mental deterioration. Because her daughter's family was next door, L.F.'s husband, who was also in his eighties, received generous help whenever he had difficulty handling her or the daily chores. However, even with these new arrangements, L.F.'s ability to care for herself continued to decline. Eventually she needed almost constant care, although she was never institutionalized because of the love and patience of her husband of more than 50 years. He outlived his wife, and, unlike her, remained intellectually sharp and physically active until a few weeks before his death at the age of 90 years.

The case history in the opening vignette describes the maternal grandmother of one of the authors (M.T.B.). Although the disease was never formally diagnosed, she surely had Alzheimer's or some similar [dementia](#). In many ways, her case was typical, characterized by loss of memory, difficulties in spatial processing, disorientation, and changes in personality, especially paranoia. The course was unremittingly downward, although she died from heat stroke before becoming totally bedridden.

In this chapter, we discuss disorders, such as [Alzheimer's disease](#), that are distinct from the neuropsychological syndromes covered elsewhere in this book. In our discussions so far, we have emphasized the breakdown of specific cognitive functions, such as visual recognition, and precisely described the circumscribed nature of the deficits. For example, in the case of visual object agnosia, we noted the specificity of the disruption, an inability to visually identify objects because of perceptual difficulties that prevent the association between visual form and meaning. However, in many clinical syndromes, including Alzheimer's disease, the breakdown of function is not restricted to one cognitive domain; rather, multiple cognitive abilities are affected simultaneously. We refer to these syndromes as [generalized \(nonspecific\) disorders](#).

You should not be surprised to learn that the causes of generalized disorders are quite different from the causes of the specific disorders we discussed in earlier chapters. Specific disorders usually result from focal damage to the brain, such as injuries caused by bullet wounds or strokes, which confine damage to the path of the projectile or the brain regions deprived of oxygen, respectively. In contrast, the causes of generalized disorders include closed head injury (which results from falls, vehicular accidents, assaults, and sports injuries), dementias (which result from pathological changes in the brain), demyelinating diseases (which result from damage to the myelin sheath surrounding neurons), and exposure to toxins, all of which are likely to have more distributed, rather than focal, effects on brain tissue.

Even though all these causes of brain damage are likely to influence more than one cognitive system at the same time, their effects are not identical, so one can observe

subtle but important differences in their neuropsychological manifestations. We now turn to a more detailed discussion of these various etiologies and the nature of the generalized cognitive disorders that they produce.

Closed Head Injury

In [closed head injury](#), the brain sustains damage because the head forcefully comes into contact with another object (e.g., a car windshield, the ground, or a blunt instrument such as a baseball bat), even though no object penetrates the brain. Closed head injury is the leading cause of [traumatic brain injury \(TBI\)](#). TBI is a more general term referring to any sudden trauma from an external source that causes damage to brain functioning (Menon et al., [2010](#)). TBI could involve a closed head injury or a scenario in which an object pierces the skull and enters the brain (penetrating head injury). TBI is a significant source of neuropsychological dysfunction, with more than 2 million new cases a year in the United States alone (Faul et al., [2010](#); Faul and Coronado, [2014](#)). This rate is higher than the combined rate of three other well-known neuropsychological disorders: Alzheimer's disease, multiple sclerosis, and Parkinson's disease.

The causes of closed head injury differ somewhat depending on age. Among adolescents and young adults, head injury is caused mainly by motor vehicle, bicycle, or vehicle–pedestrian accidents. In older people (65 years or older) and in young children, closed head injury is predominantly attributed to falls. Other causes include assault, sport-related injuries (see the “In Focus” feature), and injuries to soldiers during battle.

Alcohol is involved in some way in approximately half of all incidents of TBI (Weil et al., [2016](#)). It is not difficult to imagine the role that alcohol could play in causing car accidents, falls, and assaults. In turn, head injuries themselves can lead to an increased propensity to consume alcohol and other substances, contributing to a vicious cycle of entanglement between alcohol and head injury (Weil et al., [2016](#)).

Etiology

The primary mechanism of damage in closed head injury is a rapid acceleration of the head followed by a deceleration; thus, it is sometimes referred to as **acceleration-deceleration injury**. The energy imparted to the brain causes it to move within the skull. This movement can lead to diffuse damage as a result of the twisting and shearing of neurons, as well as focal damage due to the impact of the brain with the hard inner surface of the skull. The neurons most vulnerable to twisting are those that compose white-matter tracts, which have long axons and connect distant brain regions ([Figure 16.1](#)). This primary damage is followed by secondary biochemical effects, such as overproduction of glutamate, the brain's main excitatory neurotransmitter that leads to cell death, a phenomenon known as glutamate excitotoxicity; such effects can last for months following the primary damage (Xiong et al., [2013](#)). Edema (swelling) and inflammation can also restrict blood flow.

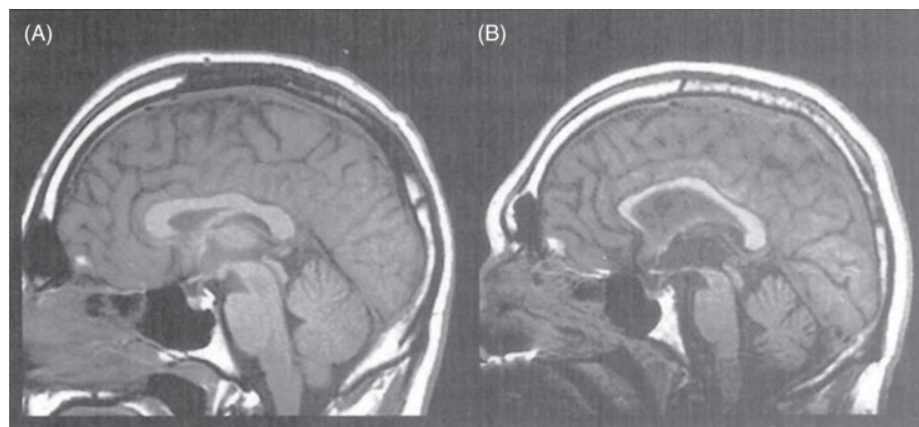


Figure 16.1 Effects of closed head injury on long myelinated nerve fiber tracts in the brain.

Compared with an age- and gender-matched neurologically intact individual (A), an individual who sustained a closed head injury (B) exhibits a neuronal loss in white matter that is especially prominent in the corpus callosum, as shown in these midsagittal MRI images.

(from Gale et al., [1995](#))

At the time of injury, such diffuse damage is not readily revealed by anatomical brain imaging studies because it does not result in a focal lesion. Instead, the major

telltale sign of closed head injury that can be detected at the time of injury is edema (swelling). As time passes, a diffuse loss of neural tissue may appear as an enlargement of the ventricles and a loss of volume in large myelinated tracts such as the corpus callosum. Diffusion tensor imaging (DTI; see [Chapter 3](#)) is now often used in research on closed head injury, because DTI is more sensitive than conventional anatomical imaging in detecting white-matter abnormalities associated with head injury (Hulkower et al., [2013](#)). Longitudinal DTI studies indicate white-matter deterioration can continue over several years following TBI, indicating a disease state that lasts beyond the initial incident. Such studies furthermore demonstrate that the degree of white-matter deterioration predicts the degree of cognitive impairment (Farbota et al., [2012](#); Salmond et al., [2006](#)).

The brain regions most likely to sustain injury are the orbitofrontal and temporal regions, because the bones at these points in the skull are rough and protrude into the cavity occupied by the brain. Focal damage at the site of impact is known as a [coup injury](#), whereas focal damage opposite the site of impact is known as a countercoup injury ([Figure 16.2](#)). For example, if the head strikes a windshield, a coup injury in the frontal areas might be sustained, as well as a countercoup injury at occipital sites.

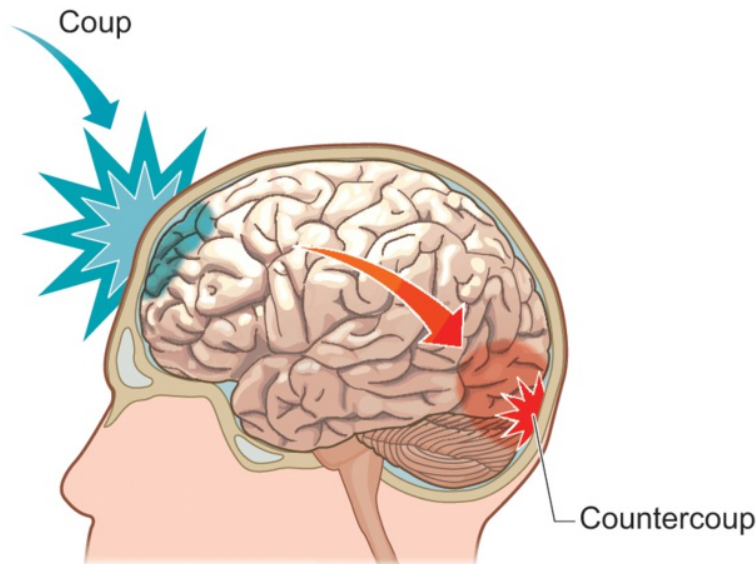


Figure 16.2 Coup and countercoup.

In closed head injuries, the brain may be damaged at the site of the impact (coup site) as well as at the site on the opposite side of the head (countercoup site).

Efforts to understand the mechanisms of closed head injury, as well as their cognitive and emotional consequences, have increased as veterans return to the United States with head injuries. For example, since 2000, approximately 300,000 American veterans of the conflicts in Iraq and Afghanistan have sustained traumatic brain injury (Helmick et al., [2015](#)). Although motor vehicle crashes and blunt trauma (hitting or being hit by an object) are the most common causes of noncombat injuries, the event typically causing injury in battle is a blast from an improvised explosive device (Galarneau et al., [2008](#)). Not only do the shock waves from the explosion cause shearing of the brain tissue, but there may also be damage if the blast hurls the person into an object or if the blast propels an object that then penetrates the brain. As in other types of brain injury, diffuse axonal damage is common (Elder and Cristian, [2009](#); Rosenfeld et al., [2013](#)).

Neuropsychological Consequences

One of the most prominent clinical signs of closed head injury is a significant alteration in consciousness. As you may remember from [Chapter 1](#), basic aspects of wakefulness

and consciousness are controlled by the brainstem. Consequently, the degree to which the injury interferes with these aspects of brainstem function can serve as a proxy for estimating the overall impact on the brain. For this reason, scales such as the [Glasgow Coma Scale \(GCS\)](#) (Teasdale and Jennett, [1974](#); Teasdale et al., [2014](#)), which assess the level of consciousness, are widely used in emergency rooms around the world. These scales provide a basic method for classifying the severity of damage in someone who has just sustained a head injury. The GCS, shown in [Table 16.1](#), evaluates three realms of functioning: visual responsiveness, motor capabilities, and verbal responsiveness.

Table 16.1 Glasgow Coma Scale Used to Predict Severity of Brain Trauma

| RESPONSE | POINTS | INDEX OF WAKEFULNESS |
|-----------------------|--------|---|
| Eye Opening | | |
| None | 1 | (Self-explanatory) |
| To pain | 2 | Response when pain stimulus is applied to chest or limbs |
| To speech | 3 | Nonspecific response to speech or shout, but does not imply that patient obeys command to open eyes |
| Spontaneous | 4 | Eyes are open, but this does not imply intact awareness |
| Motor Response | | |
| No response | 1 | Flaccid |
| Extension | 2 | “Decerebrate.” Adduction, internal rotation of shoulder, and pronation of the forearm |

| | | |
|------------------------|---|--|
| Abnormal flexion | 3 | “Decorticate.” Abnormal flexion, adduction of the shoulder |
| Withdrawal | 4 | Normal flexor response; withdraws from pain stimulus with abduction of the shoulder |
| Localizes pain | 5 | Pain stimulus applied to supraocular region or fingertip causes limb to move so as to attempt to remove it |
| Obeys command | 6 | Follows simple commands |
| Verbal Response | | |
| No response | 1 | (Self-explanatory) |
| Incomprehensible | 2 | Moaning and groaning, but no recognizable words |
| Inappropriate | 3 | Intelligible speech (e.g., shouting or swearing), but no sustained or coherent conversation |
| Confused | 4 | Patient responds to questions in a conversational manner, but the responses indicate varying degrees of disorientation and confusion |
| Oriented | 5 | Normal orientation to time, place, and person |

An individual's consciousness is assessed in three separate arenas: visual responsiveness, motor capabilities, and verbal responsiveness. The scores obtained in each of these three arenas are totaled to provide the overall score. Scores less than or

equal to 8 indicate severe head injury, scores of 9 to 12 indicate moderate head injury, and scores of 13 or greater indicate mild head injury.

Medical personnel find the GCS score useful because it has prognostic value for survival rates and the future level of functioning (see [Figure 16.3](#)). For example, a study of thousands of cases found that the survival rate for patients who scored less than 6 on the GCS was about 60%, compared to those with a score above 6, for whom the survival rate was approximately 90% (Udekwa et al., [2004](#); see also Davis et al., [2006](#)). The same study found that the GCS score at the time of injury predicted subsequent scores on a measure called the Functional Independence Measure, which assesses how well the patient is able to engage in activities like feeding and walking.

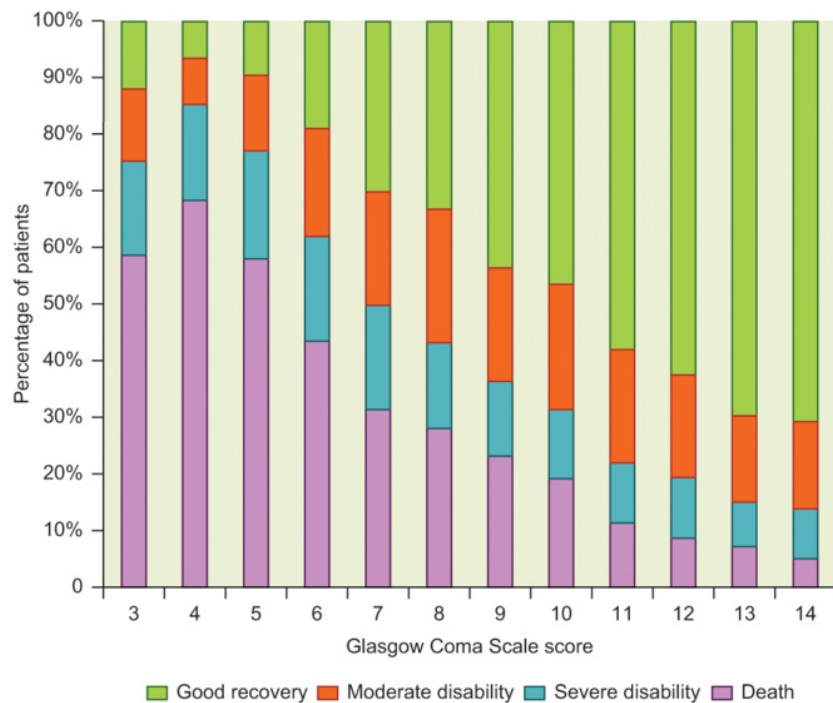


Figure 16.3 Glasgow Coma Scale scores immediately following a head injury predict the level of recovery of function six months later.

Notice that while the majority of people who sustain a mild head injury (Glasgow scores 13–14) show a good recovery (green portion of the bars), those with a moderate head injury (scores 8–12) do not fare as well, and the majority of those with severe head injury (scores <8) either die (shown in purple) or have severe disability (shown in blue).

(from Teasdale et al., [2014](#))

However, the GCS is not a perfect predictor of outcomes, as varied circumstances can make one patient's outcome better than another's outcome even if their GCS scores are the same. Furthermore, some aspects of the GCS, such as verbal responsiveness, are difficult to assess in a patient who is intubated (has a breathing tube), and other behaviors are affected by sedation. For these reasons, medical personnel also use pupil reactivity as a fundamental assessment of brainstem function in the immediate aftermath of a head injury (e.g., Majdan et al., [2015](#)). Dilated pupils that do not vary in size in response to light (referred to as fixed and dilated pupils) generally indicate a severe brain injury.

The profile of neuropsychological deficits observed after closed head injury can vary widely due to differences in the nature of the damage. Nonetheless, certain difficulties are commonly observed, most notably in memory and attention. In the realm of memory, an immediate consequence of head injury can be [posttraumatic amnesia](#), including at its most severe level an inability to report one's own name, birthdate, or address, and at less severe levels an inability to learn new information like the doctor's name (e.g., Marshman et al., [2013](#)). The initial presentation of these memory problems tends to predict the severity of injury and the subsequent level of functioning. For example, posttraumatic amnesia extending longer than three weeks is associated with a poor level of subsequent cognitive functioning.

Attention and executive functioning are also commonly affected by closed head injury (Chen and D'Esposito, [2010](#); van Donkelaar et al., [2005](#)). Although people with closed head injury maintain vigilance and alertness, they have particular difficulty in selective and divided attention, response inhibition, and cognitive flexibility. Their behavioral control is often poor, and they may appear impulsive, impatient, and distractible. In addition, the ability to plan toward a goal, or the motivation to do so, can be compromised. Motivational problems are related to emotional changes after injury, such as depression or a lack of understanding of deficits. Imaging studies indicate that alterations in attention and executive control are related to disruptions in patterns of connectivity in networks that normally support these cognitive functions, such as the default mode network and salience network (see Sharp et al., [2014](#)).

Head injuries can vary in their severity, and not surprisingly the severity of the injury affects cognitive consequences. Mild traumatic brain injury, also known as concussion, was traditionally defined by a change in consciousness for 2 to 30 minutes without other gross signs of neurological damage. However, loss of consciousness is not necessary for the diagnosis and may not even be the most common symptom (see Menon et al., [2010](#), for review of issues in mild TBI diagnosis). Other symptoms of concussion are listed in [Table 16.2](#).

Table 16.2 Frequently Observed Behaviors Associated with Mild Head Injury

| | |
|-----------------------|--|
| Vacant stare | Befuddled facial expression |
| Delayed responses | Slower to answer questions or follow instructions |
| Inability to focus | Easily distracted; unable to follow through with normal activities |
| Disorientation | Unaware of time, date, place; walking in wrong direction |
| Atypical speech | Slurred speech; incoherent, disjointed, or incomprehensible statements |
| Gross incoordination | Stumbling; inability to walk a straight line |
| Hyperemotionality | Acting distraught; crying for no reason |
| Memory deficits | Asking the same question; inability to remember what happened five minutes ago |
| Loss of consciousness | Nonresponsiveness to stimuli |

Even mild damage can have consequences for mental functioning (see Karr et al., [2014](#), for a review). Concussions, like more serious head injuries, result in a cascade of changes within the brain, including changes in neurotransmitter release, glucose metabolism, blood flow, and axonal structure and function (Xiong et al., [2013](#)). Symptoms of concussion tend to fall into three major areas. First, difficulties in cognition may be present, especially in attention, concentration, and memory. Second, the person may experience somatic symptoms, such as dizziness, blurred vision, sensitivity to noise and bright lights, sleep disturbances, fatigue, headaches, lightheadedness, alterations in taste and smell, and changes in appetite. Third, the person may undergo emotional changes, including depression, anxiety, loss of patience,

and increased temper (Riggio and Wong, [2009](#)). These symptoms can overlap with those of posttraumatic stress disorder (PTSD), which can occur together with TBI in people who experience head trauma, particularly in a military context (e.g., Alway et al., [2016](#)). Despite apparent recovery as measured by neuropsychological tests, some of these symptoms, such as irritability, anxiety, depression, insomnia, and fatigue, can persist for quite a while. Nevertheless, the prognosis for cognitive recovery is better following mild head injury compared to more severe injury (Schretlen and Shapiro, [2003](#)).

Closed head injury is a risk factor for longer-term neurological problems. First, having had a closed head injury puts a person at higher risk for sustaining another head injury, increasing the risk four to six times more than someone who has never had a head injury (e.g., Zemper, [2003](#)). The subsequent head injury may occur, in part, because some people have personality and social characteristics (e.g., risk-taking, alcohol abuse) that predispose them to accidents. However, decrements in attention and poor judgment resulting from the initial head injury may increase the probability of another head injury. For example, failing to notice a traffic light might lead to another motor vehicle accident. Likewise, post-injury changes in gait or balance could affect the likelihood of another fall. Repetitive head injury is particularly relevant in military and sports contexts, in which the occupational setting itself predisposes participants to more than one exposure to injury. Because both neuropsychological and neurophysiological effects of head injury are cumulative, the study of repetitive head injury is a critical area for ongoing research (Xiong et al., [2013](#)).

Closed head injury also raises the risk for additional neurological consequences in the future. For example, head injury is associated with posttraumatic epilepsy, which does not always manifest itself immediately but may begin more than a year after the head injury. (Later in this chapter, we discuss epilepsy in more detail.) If closed head injury occurs in early adulthood, it is associated with a significant increase in the risk of depression over the person's lifetime (Holsinger et al., [2002](#)). Furthermore, even a mild closed head injury may put an individual at higher risk for dementias such as

Alzheimer's disease (Lee et al., 2013). [Figure 16.4](#) illustrates schematically how a severe head injury – or a series of mild injuries – may affect the likelihood of developing pathology such as Alzheimer's disease.

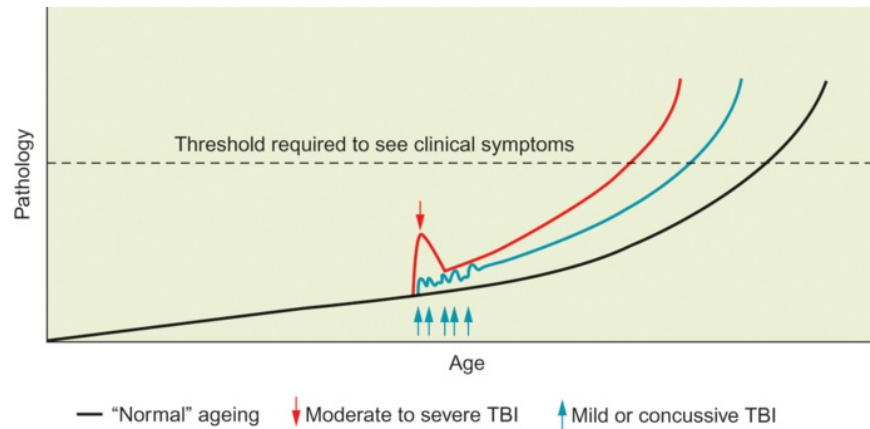


Figure 16.4 Schematic depiction of how traumatic brain injury (TBI) may alter the accumulation of brain pathology during normal aging.

According to this idea, brain pathology generally increases with age (black line). This trajectory can be affected either by a significant acute head injury (shown in red), or a series of mild head injuries (shown in blue). As a result of these injuries, there is an increased accumulation of pathology over the lifespan (compared to people who have not suffered a head injury) so that pathology is more likely to lead to clinically detectable symptoms. This figure represents only a simplified hypothesis (not actual data), and is one way of thinking about the relationship between TBI and brain pathology.

(from Smith, 2013)

Intervention

Given the prevalence of head injury and its potential consequences for individuals and families, identifying effective interventions is paramount. The best intervention is prevention: seat belts, helmets, railings, road safety, and programs to reduce alcohol abuse and violence. In addition to these efforts, recent research has examined whether

the effects of closed head injury can be addressed through treatments targeted at either the biochemical or cognitive levels.

Pharmacological treatments aim to intervene in the cascade of biochemical effects that follow a head injury, which include excitotoxicity and inflammation. Some drugs are designed to try to reduce these effects so as enhance outcomes and reduce the likelihood of seizures (Algattas and Huang, [2013](#); Rosenfeld et al., [2012](#)). While some drug treatments have demonstrated effectiveness in animal models of TBI, their relatively poor effectiveness in human clinical trials points to limitations in current knowledge (see Xiong et al., [2013](#), for review). For example, rodent models of head injury are limited both due to the model of trauma itself – it is both ethically and methodologically challenging to apply head injuries appropriately to animals – and due to the inability to assess higher-level cognitive function in rodent models.

Additional research has examined whether interventions targeted at the cognitive level can ameliorate some of the neuropsychological consequences of head injury. For example, some researchers have addressed deficits in executive functions following TBI with “metacognitive strategy instruction,” which helps patients to break problems down into steps, reason through strategies that will lead to goal achievement, and better monitor their own behavior (Tate et al., [2014](#)). Other cognitive interventions target the processes of memory and attention (Bogdanova and Verfaellie, [2012](#); Ponsford et al., [2014](#); Velikonja et al., [2014](#)). Generally, evidence suggests some degree of improvement in cognitive functioning as a result of such rehabilitative methods. However, differences across studies in the quality of research design, type of patient being studied, and outcome measures can make it difficult at present to identify best practices for cognitive intervention.

In Focus: Closed Head Injury and Sports

The controversial issue of head injuries among professional and amateur athletes has received widespread attention by American media as a critical public health

issue. For example, concerns about head injuries in American football players were featured in a popular 2013 book, *League of Denial*, by sportswriters Mark Fainaru-Wada and Steve Fainaru, and in the major motion picture *Concussion*, released in 2015. The US Congress has even held hearings on the issue of brain injuries in professional football players (Schwarz, [2009a](#)). The hearings were prompted, in part, by a study commissioned by the National Football League that found an elevated rate of early-onset dementias such as Alzheimer's among retired football players compared to the general population (Schwarz, [2009b](#)). Though these public discussions focused specifically on American football, concerns about head injuries are relevant to other contact sports as well, such as boxing, rugby, lacrosse, hockey, and soccer (called football in most of the world).

Probably the clearest case of sports-related head trauma occurs in boxing, in the syndrome known as dementia pugilistica (literally, "boxer's dementia"; McCrory et al., [2007](#)). This syndrome was first described in the 1920s and dubbed the "punch-drunk" syndrome (Martland, [1928](#)). The features typically begin to manifest at the end of a boxing career or soon thereafter, and are initially evident as tremors, slurred speech, and abnormal gait and reflexes, due to damage to the cerebellum and other motor areas. Insidiously, these difficulties become worse, and disorders in thinking and emotion emerge, indicating the extensive nature of damage to more wide-ranging regions of the brain. Regardless of whether a boxer is a professional or an amateur, heavyweight or lightweight, the probability of developing these symptoms is related to the number of bouts in which the person fought (Mortimer and Pirozzolo, [1985](#)).



Box Figure 16.1 In professional football, impacts to the head are common.

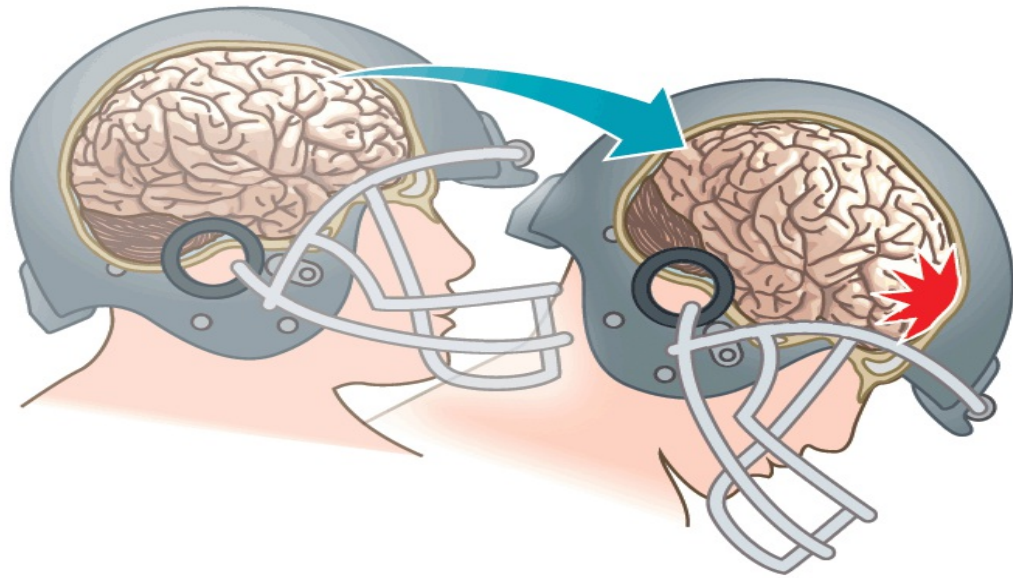
So clear is the association between head trauma sustained in the boxing ring and subsequent neurological deficits that leading neurologists have debated whether boxing should be banned (e.g., Rowland, [2006](#)). While stopping short of advocating an outright ban, the American Academy of Neurology stated in a 2008 position paper that “[s]ports that include intentional trauma to the brain (including boxing, mixed martial arts, and extreme fighting) are a serious threat to the neurologic function of those who engage in them.”

Head injuries in other contact sports tend to be associated with collisions between players, explaining why US football accounts for more than half the reported injuries. To appreciate the frequency of head trauma, consider the following: In one study of college football players, researchers found that 1 in 10 players received a head injury within any given season and that more than 40% of the athletes sustained at least one head injury during their high school and

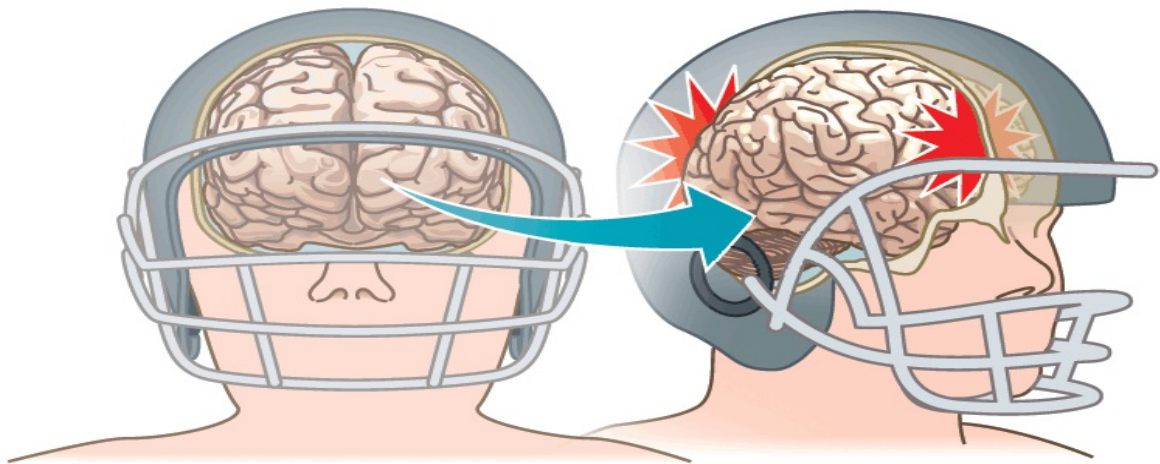
college careers (Barth et al., [1989](#)). A study of high school and college football in the US documented 28 deaths due to head and spinal cord injuries from 2005 to 2014 (Kucera, [2017](#)). Among US professional football players, 871 concussions were reported across five seasons from 2010–2014 (Clark et al., [2017](#)). Concussion rates are also high among ice hockey and rugby players, including both youth and professional players (for comparisons across sports, see Noble and Hesdorffer, [2013](#); Pfister et al., [2016](#)). These injuries occur despite the use of protective headgear.

Research on the consequences of sports-related head injuries is methodologically challenging. Obviously, researchers cannot randomly assign people to participate in sports that could lead to a concussion merely to observe the effects on their cognitive functioning. Instead, people themselves choose to participate in such sports, so researchers must rule out the possibility that preexisting factors, rather than the head injuries sustained during the sport, account for differences in cognitive functioning between athletes who play contact sports and the general population. For that reason, good studies require a carefully selected control group that is matched to the contact sports group in as many relevant variables as possible, for example, fitness level, education, and lifestyle factors such as substance use.

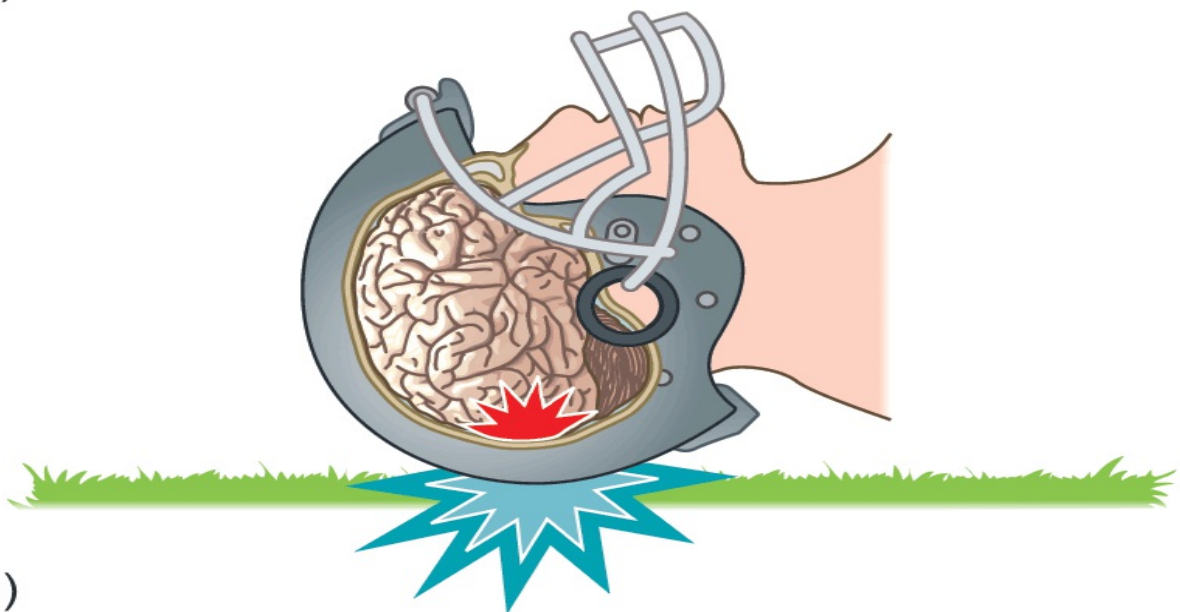
(A)



(B)



(C)



Box Figure 16.2 Different forms of biomechanical impact on the head in football.

In panel A, the brain is thrown toward the front of the skull, for example when a player is hit hard by a tackle. A countercoup impact may follow as the brain subsequently ricochets back (see also [Figure 16.2](#)). Panel B shows how the brain can also be twisted inside the skull by an impact, which can lead to shearing of nerve fibers. In panel C, the head makes an impact with hard turf when a player is tackled to the ground.

Other studies employ a pre-/post-design examining cognitive functioning in members of a team at the beginning of a season, and then again at the end of the season after some players have endured concussions. A third approach is to simply look for correlations between the number of past head injuries reported and present cognitive performance. Of course, such correlations can be difficult to interpret; for example, poor attention or slowed reflexes might lead to a head injury rather than the other way around. In addition to these study design issues, researchers must also consider whether the sample consists of amateur or professional players, who differ in their skill level and the speed and impact of play.

Despite these methodological challenges, accumulating evidence does indicate that head injuries sustained during sports can take a toll on mental functioning. Acute effects of sports-related concussion on cognitive functioning within 24 hours after the injury have been well documented, across a wide range of cognitive domains, including memory, attention, and executive function (Belanger and Vanderploeg, [2005](#)). Longer-term consequences are more subtle, but have also been documented, at least in some players. One large-scale study of more than 18,000 high school and college athletes over 10 seasons found that among those with concussions, most showed quick recovery, but about 10% showed a more prolonged period of recovery lasting up to 90 days (McCrea et

al., [2013](#)). Those with more prolonged recovery tended to be those who had more severe injuries to begin with, such as concussions that involved a loss of consciousness.

Even when a player feels that symptoms have subsided, the effect of mild head injury can still be detected in the laboratory. For example, one study examined Australian professional football players who had suffered a mild head injury, defined as any 2- to 20-minute change in consciousness with no accompanying gross signs of neurological damage, and a posttraumatic amnesia that lasted less than 24 hours (Cremona-Meteyard and Geffen, [1994](#)). The players were tested two weeks after the injury and again one year later. Two weeks after injury, they exhibited a slowing of overall reaction time and an inability to direct attention to a cued location. A year later, when the players claimed that all the behavioral signs of the concussion had disappeared, reaction times had indeed returned to normal, but the deficit in directing visual attention remained. These findings suggest that even mild head injuries may have long-term consequences.

Although the effect of head trauma on cognitive performance has been demonstrated, it is still controversial whether sports-related head injury leads to long-term pathology in the brain itself. Examination of the autopsied brains of athletes from high-contact sports such as football, hockey, and boxing has led researchers to describe a pathology known as chronic traumatic encephalopathy, or CTE (Jordan, [2013](#); Mez et al., [2013](#)). Dramatic evidence of CTE has been described in a series of cases of professional athletes who met an untimely demise, often co-occurring with severe emotional and cognitive disturbance according to family reports, clinical observation, or historical records (e.g., McKee et al., [2013](#)). CTE has a characteristic pattern of pathology at the microscopic level that includes abnormal neurofibrillary tangles and tau proteins (reminiscent of the damage described in more detail in the section on [Alzheimer's disease](#)), along with evidence of axonal injury. However, CTE is

characterized by a different pattern in the distribution of the abnormal tangles across parts of the brain, compared to Alzheimer's. Furthermore, unlike Alzheimer's, in CTE there is not always evidence of abnormal beta-amyloid plaques.

Due to the fact that CTE can only be diagnosed at autopsy, and due to difficulties in obtaining appropriate control groups, much remains unclear about the causal relationships among sports-related head injury, CTE, and mental function. To what extent can we conclude that the sports-related head injury experienced by an athlete caused the CTE evident in his brain? Correlational evidence indicating greater CTE in football players with more years of play suggests a causal connection but cannot definitively prove one (McKee et al., [2013](#)). Computational modeling of the biomechanics of a sports-related head injury predicts the most pathology in deep sulcal regions, which is where CTE tends to be most evident (Ghajari et al., 2016). This evidence again hints at a possible causal connection between head hits and CTE. Another key question, though, is whether the brains that have been autopsied are representative of all professional athletes, or whether they just represent the severe end of the continuum, those notable enough to warrant autopsy. Finally, the fact that many professional athletes in high-contact sports do not go on to develop evidence of neurodegenerative disease raises questions about whether there are additional risks or protective factors, including genetic differences, that lead some athletes' brains to respond differently to injury (Mez et al., [2013](#)).

On the pressing question of whether sports-related head injury predisposes athletes to a greater risk of dementias such as Alzheimer's disease later in life, the jury is still out. Illustrating the conflicting evidence are two epidemiological studies that point to opposite conclusions. Both of the studies relied upon clinical observation of cognition and behavior, rather than autopsy of the brain, to diagnose neurodegenerative disease. On the one hand, one study of men who

played at least five seasons in the National Football League found a three-fold increase of neurodegenerative disease among the players compared to the general population (Lehman et al., [2012](#)). On the other hand, a study of men who had played high school football in Minnesota in the 1940s and 1950s found no elevated risk for neurodegenerative disease compared to their high school classmates who did not play football (Savica et al., [2012](#)). One obvious difference between the two studies is the likelihood of repeated severe head injury when playing professionally in the NFL compared to on a high school team. Another factor is the game has become more physical in recent years, including an increase in player size, leading to increased force during impact.

What are the implications of such findings for coaches, athletes, and fans? One obvious implication is that coaches and trainers must be aware of the potential consequences of a head injury when deciding whether to put a player back into the game. A player who has suffered a concussion may be at greater risk for sustaining another head injury that will have more devastating consequences, in what is known as “second impact syndrome.” These issues are especially important for young athletes, whose brains are still developing (Graham et al., [2014](#)). Therefore, guidelines have been developed to assist coaches and trainers in determining when an injured player is ready to go back into the game (Giza et al., [2013](#); King et al., [2014](#); McCrory et al., [2013](#)). Although there is little evidence that improved helmet technology can offer increased protection against head injury, rule changes limiting head impact in both professional football and hockey could potentially reduce injuries (Noble and Hesdorffer, [2013](#)).

More broadly, professional teams must be aware of long-term medical issues that players may face in retirement, and must be prepared to offer just compensation and coverage of the related medical expenses. Players themselves should be made fully aware of the potential consequences of their choices to play bruising professional sports. Finally, fans may be sobered to realize that

what is entertainment to them – and a lucrative business for sports executives – can lead to neurological impairment in players long after they have left their days of fame and glory on the field.

Dementing Diseases

Dementia is the term for a debilitating syndrome involving a loss of cognitive functions, sometimes accompanied by personality changes, that interferes significantly with work or social activities. Although a person can become demented after an acute neurological incident (i.e., very severe head injury), dementias typically progress in stages, generally termed mild, moderate, and severe, and eventually lead to death. In mild dementia, the person retains judgment, can live alone, and can maintain adequate personal hygiene, although work and social activities are significantly impaired. As the disease progresses to the moderate stage, independent living becomes hazardous (e.g., the person forgets to turn off the stove) and some degree of supervision becomes necessary. In severe dementia, the person's abilities are so impaired that he or she requires constant supervision. For example, the person may become mute or unable to maintain minimal personal hygiene.

Dementia is a growing problem for industrialized societies, because the average lifespan continues to lengthen and the risk of dementia increases with age. Based on current rates of Alzheimer's disease and a population of older people that will swell as the baby-boom generation ages, researchers project that by the year 2050, more than 13 million people over the age of 65 will be living with Alzheimer's disease in America alone (Alzheimer's Association, [2016](#)). The burden of dementia can be staggering, both in terms of the emotional impact on families and the financial impact of long-term medical care on the health care system and economy.

Simple screening tests to evaluate the presence of dementia can be administered in a primary-care doctor's office in just a few minutes. For example, one of the most

common screening instruments, the Mini Mental State Exam (MMSE; Folstein et al., [1975](#)), includes questions about orientation to time (“What year is it? What day is it?”) and orientation to location (“What city are we in?”), as well as asking the participant to name simple objects such as a pencil or watch, to count by 7s, and to carry out simple instructions such as folding a piece of paper in half and then placing it on the table. While the MMSE may not reliably distinguish between different kinds of dementia, and may not be sensitive to milder cognitive impairment, a low score on the MMSE is a red flag indicating that follow-up tests with more sensitivity should be administered to more thoroughly evaluate the presence of dementia.

Although all dementias lead to the same depressing end, different varieties are distinct in both the specific constellation of cognitive functions affected and the course of decline. Typically, dementias are divided into three major varieties, loosely based on the region of the brain most affected: (1) cortical dementias; (2) subcortical dementias; and (3) mixed-variety dementias, which encompass both cortical and subcortical damage.

[Cortical dementias](#) manifest as the co-occurrence of many deficits that we’ve already discussed in earlier chapters, such as aphasia, apraxia, agnosia, spatial and calculation deficits, and memory problems. These dementias generally have an insidious onset in which the first symptoms are difficulty remembering events, disorientation in familiar surroundings, problems in finding the correct words to use or difficulty in naming objects. These are often accompanied by changes in personality and mood, such as apathy, which sometimes can be the first symptoms to appear. The cognitive decline thereafter is steady and slow.

In contrast, [subcortical dementias](#), such as Huntington’s disease and Parkinson’s disease, do not result in specific and striking cognitive deficits, such as aphasia and apraxia. Instead, they are much more likely to manifest first as changes in personality, slowness in the speed of cognitive processing, lapses in attention, and difficulties in accomplishing goal-directed tasks or tasks that require formation of a strategy (Bonelli

and Cummings, [2008](#)). Moreover, people with subcortical dementias have relatively few difficulties with recognition tasks, showing impairment mainly on recall. [Table 16.3](#) lists the major features that distinguish cortical and subcortical dementias.

Table 16.3 Major Characteristics Distinguishing Cortical and Subcortical Dementias

| TYPE OF DEMENTIA | | |
|----------------------|---|--|
| CHARACTERISTIC | SUBCORTICAL | CORTICAL |
| Mental Status | | |
| Language | No aphasia | Aphasia |
| Memory | Forgetful (difficulty retrieving learned material) | Amnesia (difficulty learning new material) |
| Cognition | Impaired (poor problem solving produced by slowness, forgetfulness, and impaired strategy and planning) | Severely disturbed (based on agnosia, aphasia, acalculia, and amnesia) |
| | Slow processing time | Response time relatively normal |
| Personality | Apathetic | Unconcerned or euphoric |
| Mood | Affective disorder common (depression or mania) | Normal |
| Motor System | | |
| Speech | Dysarthric | Normal* |
| Posture | Abnormal | Normal, upright* |

| | | |
|-------------------|---|---------|
| Gait | Abnormal | Normal* |
| Motor speed | Slow | Normal* |
| Movement disorder | Common (chorea, tremor, rigidity, ataxia) | Absent |

Anatomy

| | | |
|--|----------------|----------------|
| Cortex | Largely spared | Involved |
| Basal ganglia, thalamus, mesencephalon | Involved | Largely spared |

Metabolism

| | | |
|---|---|------------------------------------|
| Neurotransmitters preferentially involved | Huntington's disease: γ -aminobutyric acid | Alzheimer's disease: acetylcholine |
| | Parkinson's disease: dopamine | |

* Motor system involvement occurs late in the course of Alzheimer's disease and Pick's disease.

Mixed-variety dementias are disorders in which both cortical and subcortical involvement seem to occur. The most common mixed-variety dementia is vascular dementia (sometimes referred to as multi-infarct dementia), which results from a series of small strokes. Such dementias are observed as patterns of cognitive performance that are midway between those seen in cortical and subcortical dementias. We now turn our attention to a more detailed discussion of each syndrome.

Cortical Dementias

For each of the two major cortical dementias – Alzheimer's disease and frontotemporal dementia – we first discuss its neuropsychological profile, then its neurophysiological bases and putative causes.

Alzheimer's Disease

Most people associate Alzheimer's disease with memory loss. This association is reasonable, considering that the ability to remember a list of words after a delay is the best measure for distinguishing between a mildly demented individual and a healthy older adult, or for distinguishing between someone who is presymptomatic but later develops Alzheimer's versus someone who does not (e.g., Chen et al., [2000](#)). However, the consequences of the disease reach far beyond memory impairment. [Alzheimer's disease \(AD\)](#) is defined by a decline not only in memory but also in many other aspects of cognitive function, including at least one of the following: language, visuospatial skills, abstract thinking, motor performance, and judgment. In addition, emotional dysfunction and personality changes, which at first are subtle but later become profound, are typically observed as well. As we will learn later, the brain damage in AD is diffuse, which accounts for the broad nature of the cognitive deficits observed.

Because AD accounts for more than half of all cases of dementia in older persons (Alzheimer's Association, [2016](#)), researchers are vigorously attempting to understand both its neuropsychological consequences and its causes. Generally, AD is considered to comprise two subsyndromes. One, known as early-onset Alzheimer's, is characterized by onset of the disease before the age of 65 years, and it progresses rapidly. The other, known as late-onset Alzheimer's, is characterized by an onset after the age of 65 years, and is usually associated with a slower decline. As we discuss later, different genetic factors are linked to each of these syndromes.

At present, no specific physiological test can definitively reveal the presence of AD in living people. The defining characteristics of the disease, specific neuroanatomical changes to the brain (discussed later), can be determined only by postmortem

examination of brain tissue, so a probable diagnosis is made on the basis of behavior. When other causes of dementia have been ruled out (e.g., dementia due to substance abuse) and the person's behavioral pattern is consistent with the disease, a diagnosis of AD is made. Some research has focused on the potential for biomarkers (e.g., substances in the cerebrospinal fluid or blood plasma, or neuroimaging markers) to serve as additional indicators of disease presence (e.g., Sperling et al., [2014](#); Weiner et al., [2015](#)). However, because it has been difficult to find biomarkers that are unique to AD, the vast majority of diagnoses are made on the basis of cognition and behavior.

From its typically gradual onset, the course of the disease is progressively downward. Because of the variability of impairment seen at different stages of the disease, scales are widely used to quantify the degree to which the abilities of patients with Alzheimer's disease are compromised. For example, the Global Deterioration Scale (e.g., Reisberg et al., [1988](#), [1989](#)) uses an interview to examine memory, orientation to the world, and self-care skills to provide a seven-stage rating (from 1, no decline, to 7, very severe decline). An overview of the characteristics of each stage and its typical duration is provided in [Table 16.4](#).

Table 16.4 A Typical Rating Scale for Alzheimer's Dementia (AD)

| STAGE | DIAGNOSIS | CHARACTERISTICS | ESTIMATED DURATION* |
|-------|------------------------------|---|---------------------|
| 1 | Normal adult | No decrement noted | |
| 2 | Normal older adult | Subjective deficit in word finding and other aspects of memory | |
| 3 | Compatible with incipient AD | Deficits noted on demanding job-related tasks and may be apparent to family members | 7 years |
| 4 | Mild AD | Assistance required for complex tasks (e.g., handling finances, | 2 years |

planning a dinner party, traveling to a new location)

Person's knowledge of current and recent events diminishes

| | | | |
|---|----------------------|---|-----------|
| 5 | Moderate AD | Assistance required for many daily tasks | 18 months |
| | | May not know the day, location, or time | |
| | | Is likely to still remember family member | |
| 6 | Moderately severe AD | a. Assistance required for dressing | 5 months |
| | | b. Assistance required for proper bathing | 5 months |
| | | c. Assistance required with mechanics of toileting (e.g., flushing, wiping) | 5 months |
| | | d. Urinary continence lost | 4 months |
| | | e. Fecal continence lost | 10 months |
| 7 | Severe AD | a. Speech ability limited to about one-half dozen intelligible words | 12 months |
| | | b. Intelligible vocabulary limited to a single word | 18 months |
| | | c. Ambulatory ability lost | 12 months |
| | | d. Ability to sit up lost | 12 months |

| | |
|---------------------------------|-----------|
| e. Ability to smile lost | 18 months |
| f. Ability to hold up head lost | Unknown |

* In patients who survive and progress to the next stage.

Recently researchers have focused on a related disorder, [mild cognitive impairment](#) (MCI), which is characterized by a cognitive decline that is greater than typical for a person's age, but not sufficiently severe to warrant a diagnosis of dementia (for review, see Petersen et al., [2014](#)). People with MCI, estimated to be about 15–20% of the population over age 65, exhibit decline that may be noticeable to the patient, family members, or close friends, but is not severe enough to interfere with daily functioning. Currently, scientists are debating whether MCI represents an early stage of AD or a distinct condition. On the one hand, people with MCI have a greater risk of developing full-blown AD compared to age-matched control participants who do not have signs of MCI (e.g., Roberts et al., [2014](#)). Yet, not all people identified with MCI go on to develop AD, so there must be additional factors – as yet unknown– that determine whether a person's path will lead from MCI to AD (Ganguli et al., [2011](#); Summers and Saunders, [2012](#)).

Neuropsychological Profile

Typically, complaints of memory problems are the reason a potential Alzheimer's patient first comes to the attention of a physician. People with AD have an inability to acquire new information, and therefore show a severe and global anterograde amnesia (see Minati et al., [2009](#), for a review). Not surprisingly, at least in the earlier stages of the disease, there can be significant discrepancies between their IQ scores (which tend to rely more on previously acquired information) and their scores on tests that measure the acquisition of new information.

People with AD instinctively remain in familiar environments and engage in routine behaviors, reducing the need to acquire new information. As a result, the severity of the

deficit may become evident only when the person is placed in unfamiliar circumstances. For example, while a person with AD may appear to have no difficulty getting back home from the familiar neighborhood grocery store, returning from the pool to a hotel room while vacationing at a new resort may be impossible.

Although patients with AD exhibit amnesia, the pattern of memory impairment differs in important ways from typical medial temporal lobe amnesia (see [Chapter 9](#)) because the brain regions affected go beyond medial temporal regions to affect cortical processors as well. Procedural knowledge and implicit learning are not spared in those with Alzheimer's disease, unlike in typical amnesic patients. As discussed in [Chapter 9](#), procedural memory is independent of the hippocampal system and depends on activating the same cortical processors that were used in the acquisition of a skill. Furthermore, unlike typical amnesic patients, patients with more severe AD also exhibit extensive retrograde amnesia and may have problems with working memory, as reflected in poor performance on digit span tasks.

Language problems are also evident throughout the different stages of AD, affecting verbal fluency and semantic aspects of language more than syntax or phonology (Verma and Howard, [2012](#)). At later stages, the patient's speech becomes sparse and empty of meaning. For example, when asked to name an orange pictured in a photograph, a moderately demented patient replied, "Same thing, this is no, no, they may be this here and it didn't get here, but it got there, there, there" (Bayles, [1982](#), p. 276). Despite the lack of content, the syntactic structure of these patients' language remains intact, and they show few phonemic disturbances or articulatory problems. Patients with AD also exhibit difficulty in other functions, such as visuospatial processing, conceptual aspects of motor behavior (similar to apraxia), and executive functions. The exact functions compromised, especially in the early phases of the disorder, vary from patient to patient, but the overall picture is one of generalized, rather than function-specific, decline.

Alzheimer's disease also causes changes in emotional functioning and personality. Caregivers describe that compared to their premorbid personalities the patients are more neurotic, vulnerable, and anxious; less extroverted; more passive; less agreeable; less open to new ideas; and more depressed, though not profoundly so. However, patients with AD generally do not exhibit odd or socially inappropriate behaviors, which are more common in people with subcortical dementias. Nonetheless, at later stages of the disease, delusions, especially of persecution, infidelity, and theft, may occur, as discussed in the opening vignette.

Some research has examined whether subtle cognitive deficits can be detected in those at risk of developing AD even before they would normally experience symptoms that would lead them to seek medical attention (e.g., Rentz et al., [2013](#)). The focus on such "pre-clinical" signs of impending cognitive decline is motivated by the idea that earlier knowledge of decline could lead to earlier intervention, potentially benefiting the patient. But detecting subtle decline is challenging because it requires cognitive tests that are sensitive enough to distinguish performance in "pre-clinical" AD from performance that characterizes normal aging. Many of the tests currently under consideration for this purpose involve tasks of associative binding, such as learning to associate arbitrary pairs of words or pairs of names and faces. Other tasks being studied include a pattern separation task, in which participants engage in an old/new recognition task ("Did you see this picture in the previous list?") with lures that are highly similar to the previously viewed items, taxing the specificity of memory encoding. As you may remember from [Chapter 9](#), these are exactly the sorts of tasks that rely heavily on the hippocampus. Preliminary evidence suggests that performance on such tasks is altered in nondemented people who are at high risk for developing AD based on genetic risk or evidence of elevated levels of amyloid plaques, a physiological feature characteristic of AD (as explained further below) (Rentz et al., [2013](#)).

Neurophysiological Bases

One of the main challenges in Alzheimer's research is characterizing the pathological features of the brain and determining which of these features reflects the essential cause of the disorder. Great progress has been made in describing the pathology, but understanding of the causal chain that leads to the presence of these pathological features has been more elusive (for a review of Alzheimer's pathology, see Perl, [2010](#)).

The defining neurobiological characteristic of Alzheimer's disease is a brain riddled with large numbers of neurofibrillary tangles and amyloid plaques. [Neurofibrillary tangles](#) are twisted pairs of helical filaments found within the neuron (see [Figure 16.5](#)). They are similar to but distinct from microtubules, which are normal cell structures that allow neurotransmitters and other proteins made within the cell body to be transported to other regions of the cell. Because of their structure, neurofibrillary tangles are thought to disrupt a neuron's structural matrix. Although these tangles can be found in the brain of the average healthy older individual, they are found in greatly increased numbers in the cortex of an individual with Alzheimer's disease.

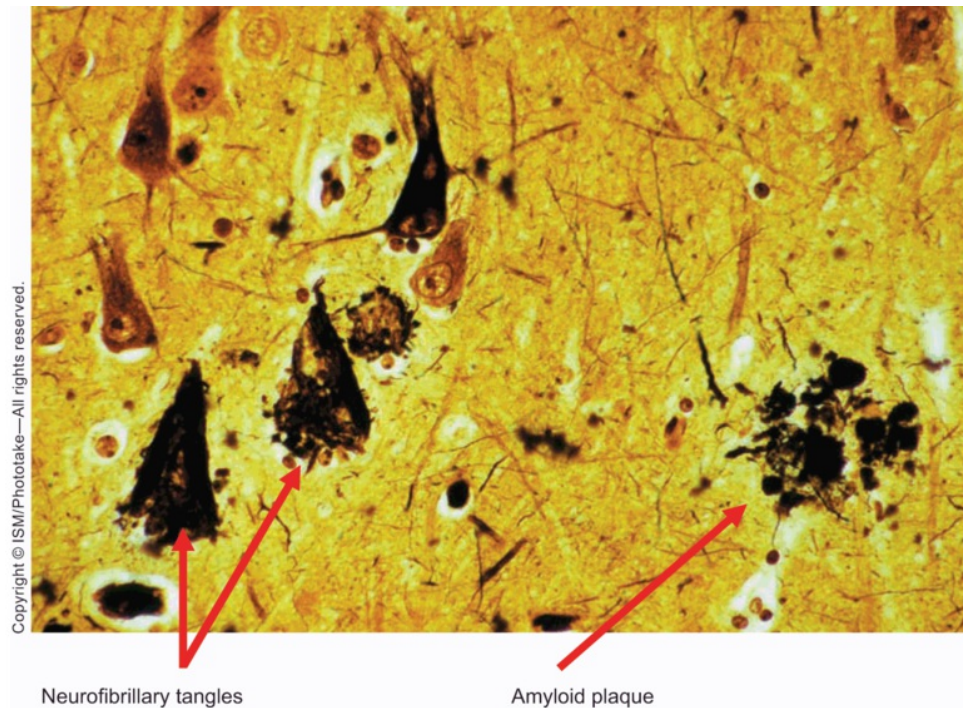


Figure 16.5 Neurofibrillary tangles and plaques that are typically observed in Alzheimer's disease.

Shown here is a section of cortex from a patient with Alzheimer's disease. The neurofibrillary tangles are the dark cone-shaped objects, and the plaques are the brown clumps.

Source: ISM/Phototake.

Neurofibrillary tangles are not equally distributed throughout the brain: they show an affinity for medial temporal, inferior parietal, and frontal regions, while sparing primary motor and sensory areas. Anatomical research has shown that tangles and plaques are first noted in the regions at the base of the brain along the midline, and they seem to spread out from there (Mesulam, [2013](#)). This pattern has led some researchers to suggest that whatever destructive process affects people with AD appears to propagate across the brain. However, because large numbers of neurofibrillary tangles are also observed in other neurological conditions such as Down syndrome, dementia from boxing, and Parkinson's disease resulting from encephalitis, their role in causing AD is still uncertain.

Amyloid plaques are deposits consisting of aluminum silicate and amyloid peptides, meaning that they are basically a buildup or a conglomeration of proteins ([Figure 16.5](#)). These plaques often include tau protein and apolipoprotein E (ApoE), which, as we will soon learn, are implicated in the genetic aspects of Alzheimer's disease. The plaques, typically surrounded by neurons containing neurofibrillary tangles, are believed to cause vascular damage and neuronal cell loss. The accumulation of tau protein appears to be especially important in contributing to cell death, so intense research has focused on attempting to understand the molecular mechanisms of tau accumulation (Spires-Jones et al., [2009](#)).

As with neurofibrillary tangles, amyloid plaques can be observed in the brain of the average older person without dementia. What distinguishes people with Alzheimer's disease from the neurologically intact older population is the number of plaques, which tend to concentrate in the cortex and the hippocampus. As with tangles, debate continues as to whether amyloid is the cause of Alzheimer's disease, the way a virus might cause the flu, or a by-product of the disorder, much as a fever accompanies the flu but does not cause it (Jagust, [2016](#)).

In the past, plaques and tangles could only be detected upon microscopic examination of the brain at autopsy. This made it hard for scientists to examine the relationship between cognitive function and the underlying changes in brain structure. However, recent developments in imaging methods, particularly PET methods involving a ligand that binds to amyloid, have made it possible to assess the presence of amyloid plaques in a living person (Adlard et al., [2014](#)). Such imaging methods are not yet reliable enough for use by doctors in considering the diagnosis or treatment of patients, but rather are being used solely for research purposes. Nevertheless, initial evidence from a longitudinal study indicates that progressive accumulation of amyloid plaques, as measured by such imaging methods, is associated with cognitive decline in living AD patients as well as those with MCI (see [Figure 16.6](#); Villemagne et al., [2013](#)). These

findings illustrate the potential that such imaging may play in future studies of the disease and possibly even as a tool for diagnosis.

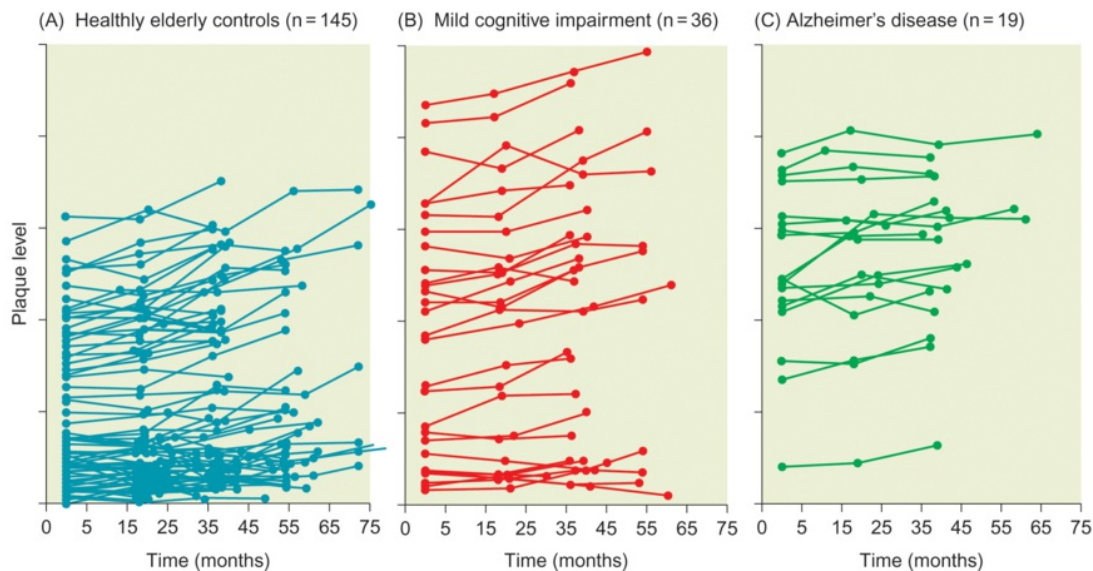


Figure 16.6 Accumulation of amyloid plaques in a longitudinal study of living patients using PET imaging.

Shown on the x axis is the time since initial enrollment in the study. Shown on the y axis is the degree of accumulation of amyloid. Each set of dots connected by lines represents a different individual. Across all three groups – healthy controls, patients with mild cognitive impairment, and those with Alzheimer’s disease – plaques tended to increase over the course of the study. On average, plaque presence was lowest in the healthy controls, intermediate in those with MCI, and highest in those with AD. However, there is notable variability across people within each group, illustrating the difficulty in using amyloid plaque presence as a diagnostic criterion for AD. Across all groups, the rate of plaque accumulation correlated with a decline in memory performance over time.

(from Villemagne et al., [2013](#))

The net result of accumulating tangles and amyloid plaques is the loss of synapses and then the loss of cells. At later stages of the disease, the cell loss is very visible on anatomical brain images, as the cortex is atrophied and the ventricles enlarged ([Figure 16.7](#)). As might be expected from the description of the location of tangles and plaques,

cell loss in the cortex is widely distributed across frontal, anterior temporal, and parietal regions (e.g., Arendt, [2009](#); Du et al., [2007](#)). The subcortical and midbrain structures most affected include the hippocampus, amygdala, and olfactory system. The amount of cortical thinning measured with structural MRI can predict symptom severity even in early stages of the disease (Dickerson et al., [2009](#)). Furthermore, the pattern of cortical atrophy is associated with the domains of cognitive decline, with greater temporal lobe atrophy associated with greater decline in memory, and more widespread cortical atrophy associated with greater decline in executive functions (Zhang et al., [2016](#)). Therefore, although gray-matter loss is not the original cause of the disease, it is closely associated with the characteristic cognitive decline of the disease.

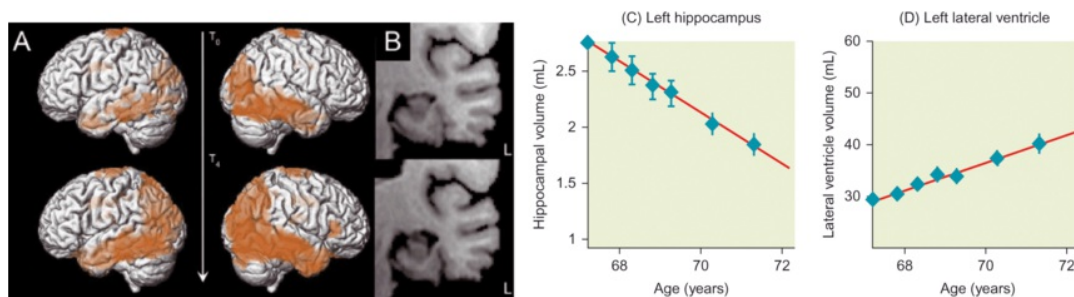


Figure 16.7 Gray-matter loss over a period of four years in an Alzheimer's patient. Panel A illustrates cortical regions that exhibited volume loss, and panel B illustrates volume loss in the hippocampus specifically. Panels C and D show the linear decrease in hippocampal volume and corresponding increase in ventricular volume during the four years of the study.

(from Jahn, [2013](#))

Beyond examining regional gray-matter loss, recent studies have also examined the effect of AD on functional connectivity within brain networks (Dennis and Thompson, [2014](#); Pievani et al., [2011](#)). Of particular interest have been patterns of activity in the brain's intrinsic networks (also called the default mode network), that is, the regions that are consistently co-activated during resting states in normal participants (e.g., Binnewijzend et al., [2012](#)). For example, the pattern of amyloid plaque accumulation across cortical regions in AD closely maps onto the regions implicated in the default

mode network as well as frontal-parietal attention networks. Indeed, one study found that plaque accumulation predicted the extent to which functional connectivity (co-activation across regions) was reduced in these networks in AD (Myers et al., [2014](#)). Thus, although the pathology of AD may begin on the cellular and molecular level, the consequences of that pathology extend to larger-scale systems of regional brain activity in ways that can impact cognition.

Genetic Bases and Risk Factors

Much research has examined genetic factors that are related to Alzheimer's disease. One set of genetic factors involves mutations that lead to Alzheimer's disease. They are associated with early-onset Alzheimer's dementia and all involve increased production of the amyloid beta protein. Another set of genes is associated with the risk of late-onset Alzheimer's disease, either increasing or decreasing the likelihood of disease. These genetic contributions to Alzheimer's disease are outlined in [Table 16.5](#).

Table 16.5 Genetic Associations for Alzheimer's Dementia (AD)

| Gene | Chromosome | Effect |
|-----------------------------|------------|---|
| Mutations Causing AD | | |
| Presenilin 2 | 1 | Disease typically occurs between age 30 and 40 years, but can be wide-ranging |
| Presenilin 1 | 14 | Disease occurs between age 50 and 65 years |
| Trisomy 21 (Down syndrome) | 21 | Disease occurs between age 30 and 40 years |
| Amyloid precursor protein | 21 | Disease occurs between age 40 and 50 years |

Factors Modulating AD

| | | |
|--------------------------------|----|---------------------------------|
| Apolipoprotein – ApoE-4 allele | 19 | Increased risk of late-onset AD |
| Apolipoprotein – ApoE-2 allele | 19 | Decreased risk of late-onset AD |

A number of genes have been found to cause early-onset Alzheimer's disease. For example, scientists estimate that more than 85% of people with early-onset dementia evident across multiple generations of a family have one of three gene mutations: the APP, presenilin 1, or presenilin 2 mutation (see Bertram and Tanzi, [2008](#); Loy et al., [2014](#), for reviews). All of these mutations affect the accumulation of amyloid plaques.

APP is a mutation of the gene on chromosome 21 coding for amyloid precursor protein, and aberrant breakdown of this protein is linked to the formation of amyloid deposits. Interestingly, by the age of 30, individuals with Down syndrome, which involves an extra copy of chromosome 21, have pathology of the brain similar to that seen in people with Alzheimer's disease and start to exhibit dementia with increasing age (Lott and Dierssen, [2010](#)).

In addition to the APP gene mutation, the other two mutations that are linked to early-onset AD involve the protein presenilin (literally, “pre-senility” mutations), which also affects the accumulation of amyloid plaques. While these genetic mutations are strongly associated with early-onset varieties of AD, early-onset cases account for less than 5% of all patients with AD. Thus, additional research is needed to understand genetic contributions in the more typical late-onset type.

The gene that has been most closely associated with the risk of getting Alzheimer's disease is the ApoE gene, which codes for apolipoprotein E, a protein that is thought to play a role in clearing amyloid plaques (for reviews, see Donix et al., [2012](#); Loy, 2014). Commonly the gene has three alleles (i.e., possible forms): e-2, e-3, and e-4.

The ApoE-4 allele is associated with an increased risk of Alzheimer's. For example, this allele is present in approximately 15% of the general population but in 40% of patients with Alzheimer's, and people with one copy of the allele are three to four times more likely to develop Alzheimer's than participants without any ApoE-4 alleles (Bu, [2009](#)). Interestingly, the presence of the ApoE-2 allele, which is relatively rare, seems to be associated with a decreased risk of developing the disease.

The presence of the higher-risk ApoE-4 allele appears to affect the degenerative course of the disease. For example, among Alzheimer's patients, those who possess the ApoE-4 allele show faster rates of hippocampal atrophy compared to those with no alleles of this type (Schuff et al., [2009](#)). In addition, Alzheimer's patients with the ApoE-4 allele have greater levels of amyloid plaque accumulation than do those with other genotypes (Drzezga et al., [2009](#)). However, the ApoE-4 genotype cannot solely account for the development of Alzheimer's characteristics. For example, having a family history of AD is associated with reduced cortical thickness in temporal lobe regions even once the presence of the ApoE-4 allele is statistically controlled (Donix et al., [2010](#)), implying that additional genetic or environmental factors that are shared within families must also play a role.

Factors other than genes have also been linked to the risk of developing Alzheimer's (Alzheimer's Association, [2016](#)). Factors that increase risk include smoking, cardiovascular disease, diabetes mellitus, and head injury. On the other side of the coin, other factors are associated with decreased risk of Alzheimer's disease. These include higher education, involvement in mentally challenging activities, social engagement, and high levels of physical activity (Beydoun et al., [2014](#); Karp et al., [2006](#); Scarmeas et al., [2009](#)). Epidemiological studies have also found that people who adhere to a Mediterranean diet (lots of fruits, vegetables, fish, and olive oil, with low saturated fat intake) have a reduced risk of developing dementia and a lower mortality rate if Alzheimer's is diagnosed (Lourida et al., [2013](#)).

Cognitive abilities prior to the elderly years also seem to predict risk for dementia. For example, in one study of elderly nuns, the complexity of a nun's writing exhibited 50 years earlier, when she first entered the convent, predicted her likelihood of getting Alzheimer's in old age (Snowdon et al., [1996](#)). One possibility is that the processes leading to Alzheimer's may start at an early age and accumulate over a lifetime. Alternatively, these results might provide evidence for [cognitive reserve](#), which is the idea that people with greater mental capacity can sustain more insult before exhibiting symptoms (Stern, [2012](#)). For example, some people may just be endowed with a greater-than-average elaboration of dendritic branching and synaptic density. Their brains can sustain more degradation before the damage to the matrix of their synaptic connections makes them incapable of handling complex cognitive thought.

Treatment and Prevention

At present, no treatment can cure Alzheimer's disease. At best, treatments may postpone the cognitive decline for some period of time. Given the staggering cost of the condition and the numbers of people affected, enormous effort is currently being invested in attempting to discover new approaches that could potentially yield a more effective treatment. For example, the Alzheimer's Association ([2016](#)) reports that between 2002 and 2012, more than 200 drugs were tested in clinical trials for possible beneficial effects on AD, yet only one of those successfully completed clinical trials and was approved for use by the US Food and Drug Administration.

The vast majority of therapeutic interventions for Alzheimer's disease attempt to influence the cholinergic system, because acetylcholine levels are linked to the severity of memory loss and dementia. The main route for cholinergic input to the cortex and hippocampus occurs via a relatively small structure called the nucleus basalis of Meynert, which is located near the base of the brain, where neurofibrillary tangles often first appear (Mesulam, [2013](#)). As the tangles lead to cell death in this structure, the rest of the brain becomes starved of acetylcholine. Therefore, drugs that have been most commonly used to treat Alzheimer's disease – such as donepezil, rivastigmine, and

galantamine – all attempt to increase availability of acetylcholine (see Anand and Singh, [2013](#); Fuentes, [2009](#), for reviews). These drugs inhibit the action of acetylcholinesterase, the enzyme that breaks down acetylcholine in the synaptic cleft. In addition to these drugs, another drug used to treat Alzheimer's disease is memantine, which blocks NMDA receptors. This drug reduces the neurotoxicity that is induced by excess levels of excitatory amino acids in Alzheimer's disease.

These drugs can slow the course of AD, but they do not stop its progression, most likely because they do not directly address the core pathology of AD, namely, the formation of plaques and tangles. However, slowing the progression of the disease can have a real-life impact, such as delaying the time until the patient is admitted to a nursing home (Howard et al., [2015](#)). Although this benefit may seem at first glance to be rather trivial, a delay in nursing home placement can be very important. For the affected person and his or her family, it provides time to make the necessary financial, living, social, and emotional adjustments to prepare for the patient's decline. For society as a whole, it can mean tremendous financial savings both in direct costs, such as nursing home, acute, and in-home care; and indirect costs, including unpaid home care provided by family and friends.

Researchers continue to search for new drugs in the hopes of further slowing or even stopping the degeneration that is characteristic of Alzheimer's disease. Some candidate drugs attempt to influence the core pathology of amyloid plaque deposition and tau protein formation (e.g., Brunden et al., [2009](#); Salomone et al., [2012](#)). Others address different steps in the pathological cascade of events. For example, some anti-inflammatory drugs are being investigated, because plaque formation is associated with inflammatory processes. Antioxidant drugs are also under study because they protect against oxidative stress that damages cells. In addition, neurotrophic drugs, such as nerve growth factor, may be useful because they can stimulate the growth of new neurons and therefore protect against cell loss.

Research has also focused on possible avenues for prevention. Because mild cognitive impairment (MCI) is viewed as a potential precursor to Alzheimer's disease, it is being investigated intensely. The hope is that a better understanding of MCI will yield insights into the early pathophysiology that might lead to Alzheimer's disease, as well as to identification of people who might benefit from early intervention (Petersen and Negash, [2008](#)). Some researchers have focused on finding ways to identify early accumulation of plaques before cognitive-behavioral symptoms even develop, in the hopes that intervention could be beneficial at that time point (Sperling et al., [2014](#)). Furthermore, because lifestyle factors – such as diet, exercise, smoking, and engaging in social and mentally challenging leisure activities– are associated with the likelihood of disease, prevention methods focused on lifestyle choices are also warranted. It may be that you can start making choices now that will reduce your chances of getting Alzheimer's in your eighties!

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a cortical dementia, like Alzheimer's, but it differs from Alzheimer's with regards to age of onset, symptom profile, and the brain regions most affected. The average age of onset in FTD is approximately 56–58 years of age, much younger than is typical in AD (Mendez, [2006](#)). As a result, FTD accounts for about 10% of dementia cases under the age of 65, and only about 3% of cases over the age of 65 (an age range in which AD is even more dominant; Hogan et al., [2016](#)). FTD is also sometimes referred to as Pick's disease or frontotemporal lobar degeneration.

Two main subtypes of FTD have been characterized, referred to as behavioral-variant FTD and primary progressive aphasia (or semantic aphasia; Warren et al., [2013](#)). As you can surmise from their names, the behavioral variant primarily involves inappropriate behavior and personality changes, whereas primary progressive aphasia primarily involves progressive decline in language (e.g., breakdown in vocabulary knowledge).

In patients with the behavioral variant, the most striking symptom is a lack of inhibitory control, especially in the realm of social-emotional functioning (Mendez, [2006](#)). People with this kind of dementia may act impulsively, for example snatching food off someone's plate or shoplifting. They may swear at inappropriate times, have outbursts of frustration, and exhibit inappropriate sexual behaviors. Their lack of concern for social norms usually extends to their personal appearance and hygiene. Furthermore, they have little or no insight into or awareness of the inappropriateness of their behavior. Another characteristic that is sometimes observed is a preoccupation with repetitive or routinized behavior. FTD patients may read the same book over and over again or always take a walk to the same place. In addition, they can be hyperoral, overeating and obsessively focusing on food. Mood changes can occur as well, tending toward depression and anxiety. Most of these symptoms are observable clinically without need for cognitive testing. If testing is undertaken, patients may perform normally on some tasks of executive functioning (such as card sort tasks), while showing deficits specifically on tasks of inhibitory control (O'Callaghan et al., [2013](#)).

Patients with the primary progressive aphasia subtype, in contrast, mainly exhibit difficulties in the domain of language. People with this variant of FTD tend to have difficulty in verbal expression and in naming of persons and things. With time, their speech has less and less content, and eventually they can become practically mute. Difficulties in reading and writing also develop. Later in the disease, they may have Parkinson-like motor difficulties, with tremor and rigidity.

In both variants, other aspects of mental functioning, however, remain surprisingly intact. For example, spatial cognition and higher-order motor programming seem to be relatively preserved in those with FTD. In one case report, a former computer engineer took to wandering miles from his home to collect cans, and never had any trouble returning home. However, his wife had to start managing his behavior when he started peering into people's windows in search of his prized cans! Memory problems are less prominent at first (in stark contrast to AD), as FTD patients tend to be oriented to time

and place and are able to keep track of recent events, at least in the initial stages of the disease. However, although memory is not the dominant complaint as in Alzheimer's Disease, memory dysfunction does occur in FTD as well (e.g., Frisch et al., [2013](#); Hornberger and Piguet, [2012](#)).

Based on what you've learned earlier in this text, it should not be surprising that deterioration of frontal and temporal lobes would have effects on impulse control, emotion, and language, although you might hazard a guess that different subregions of the frontal lobes may be involved in the two subtypes. For example, the behavioral variant appears to be characterized by anterior temporal as well as orbitofrontal damage, whereas the progressive aphasia variant involves more specific left-sided anterior temporal deterioration (e.g., Mesulam et al., [2014](#)). Nevertheless, there is symptom overlap between the two variants, as those with progressive aphasia will often develop behavioral symptoms as well, and those with the behavioral variant often have difficulty with verbal fluency. Notably, the distribution of cell loss in FTD appears to follow a different pattern than in Alzheimer's disease. Whereas patients with AD have thinning across all major cortical regions (frontal, temporal, parietal, and occipital), patients with FTD have characteristic thinning primarily in frontal and anterior temporal regions, with less thinning in the parietal lobe than Alzheimer's patients (Du et al., [2007](#)). The relative preservation of parietal cortex likely accounts for relatively preserved spatial cognition. In addition, patients with FTD have greater loss of white matter in the frontal lobes than do patients with Alzheimer's disease (Zhang et al., [2009](#)). [Figure 16.8](#) illustrates an example of the severe atrophy of the frontal regions in FTD.



Figure 16.8 Brain atrophy in frontotemporal dementia.

Note the much more severe degeneration in the frontal regions relative to that in other areas of the cortex.

(from

http://images.radiopaedia.org/images/4972/74a1b3970176517ab4696a566a8802_galle

Frontotemporal dementia differs from AD not only in the location of damage, but also in the abnormal cellular characteristics within those damaged regions. Generally, FTD is characterized by abnormal protein deposits within neurons. For example, FTD is often characterized by two main features: pale neurons swollen as if they had “ballooned,” and clumps of fibers in the cytoplasm that are stained by silver and are known as Pick’s bodies. These fibers are distinguishable from the neurofibrillary tangles of Alzheimer’s disease because they are straight rather than paired and helical.

The largest risk factor for FTD is the presence of the same dementia in a closely related family member. This pattern suggests a strong genetic component, though researchers are still working to identify the exact genetic mechanisms that give rise to the disease. Genes that are linked to FTD include a gene coding for the tau protein, as well as other genes coding for pathological proteins in FTD (e.g., progranulin and TAR

DNA-binding protein 43; Mendez, [2006](#); Rademakers et al., [2012](#)). Progress in identifying gene mutations associated with FTD has been so rapid that subtypes of the disease are now being classified based on the genetic mutation present. Interestingly, the ApoE genotype is not as strongly associated with risk for FTD as it is for Alzheimer's, again pointing to different causes of the two diseases.

One similarity between FTD and Alzheimer's is that, sadly, no cure exists for either one. Pharmacological approaches that can slow the course of AD, such as cholinesterase inhibitors, appear to have no beneficial effect on FTD. Clinical approaches focus on helping patients and their caregivers manage the symptoms and make plans for the future. This may be especially critical because, more so than in AD, patients with FTD even in the early stages often have little self-awareness of the severity of their symptoms, and disinhibited behaviors may pose safety risks to the patients and those around them. Furthermore, support for caregivers is essential because, especially in the behavioral variant of FTD, the patients' personality changes and inappropriate behavior can cause them to seem almost unrecognizable to caregivers, increasing the stress involved in managing this progressive disease. Future interventions to address the disease will depend upon better understanding of the pathology of the disease at the molecular level (Rademakers et al., [2012](#)).

Subcortical Dementias

Patients with subcortical dementias display a pattern of cognitive disabilities that is distinct from those observed in patients with cortical dementias. Thought tends to be slowed, and symptoms related to frontal lobe dysfunction are prominent. These latter difficulties probably result because the main subcortical regions affected in these dementias have intimate connections with frontal regions. Here we discuss two subcortical diseases: Parkinson's and Huntington's.

Parkinson's Disease

As we learned in [Chapter 4](#), patients with Parkinson's disease have a specific cell loss in the substantia nigra, the major source of dopaminergic neurons in the brain, and to a lesser degree in the locus coeruleus. Along with the motor symptoms that accompany the disease, dementia is evident in approximately 30% of Parkinson's patients, and others exhibit mild cognitive impairment that may develop into dementia during the course of the disease (e.g., Broeders et al., [2013](#); Svenningsson et al., [2012](#)). Because we already examined motor symptoms of Parkinson's disease in [Chapter 4](#), we focus here on cognitive symptoms that are associated with Parkinson's dementia. These symptoms include dysfunction of executive processes, slowing in motor and thought processes, and impairment in memory encoding and retrieval.

Patients with Parkinson's disease exhibit difficulties in the realm of executive function (e.g., Aarsland et al., [2011](#); Dirnberger and Jahanshahi, [2013](#)). For example, these patients have difficulty with tasks like the Wisconsin Card Sort Task, not so much because they act in a perseverative manner but because they are not able to think abstractly, being deficient at identifying the categories into which the cards should be sorted. They also exhibit deficits in switching between categories, in overriding stereotypic responses, in responding to novel situations, and in developing plans of action. Furthermore, Parkinson's patients exhibit deficits in both memory encoding and retrieval processes that are thought to be dependent on the frontal lobes (e.g., Brønneck et al., [2011](#); MacDonald et al., [2013](#)).

A second area of cognitive compromise exhibited in Parkinson's disease is the general slowing of motor and thought processes known as [bradyphrenia](#) (Mahurin, [2008](#)). Although patients with Parkinson's disease can arrive at a correct answer, they do so slowly, as if they need to overcome some sort of mental inertia. Slowing is more likely to occur on tasks requiring planning (e.g., Tower of London) than on simpler tasks. This slowness may influence a variety of mental functions, contributing to poor performance in other domains, such as language and visuospatial functioning. For example, mental slowing can reduce the ability to name items and can disrupt

articulatory capacities. Some of the slowing of mental and motoric functions may also be exacerbated by the depression that often accompanies the disease.

Patients with Parkinson's disease also show changes in emotion (Borek et al., [2006](#); Narme et al., [2013](#)). Approximately 40–50% of Parkinson's patients exhibit depression. This depression appears to be linked more to the neurobiological substrate of the disease than to the disabilities imposed by the illness. Levels of depression in patients with Parkinson's disease are higher than those observed in patients with other debilitating motor impairments, such as paraplegia and hemiplegia. Also, the depression may precede motor symptoms and be uncorrelated with their severity. Another prominent symptom is the [Parkinsonian mask](#), which is an expressionless face. This mask-like facial appearance may, in part, reflect a dampening of motor movements, but it may also reflect a dampening of emotional responsiveness. The facial expressions and tone of voice of people with Parkinson's disease lack emotional intensity, even in response to pictures with strong affective value.

Many of these cognitive and emotional deficits associated with Parkinson's disease are predictable, due to the deficient dopamine that normally flows upward through the dopaminergic path from the midbrain to both subcortical and cortical regions of the frontal lobe (Narayanan et al., [2013](#)). For example, compromise of the dopaminergic system may explain some of the apathy and lack of pleasure associated with depression in these patients, because dopamine is critical to the brain's subcortical reward system. In addition, dopamine in the prefrontal cortex is thought to be important in executive functions (see [Chapter 11](#)), so it follows that disrupted dopamine input to the prefrontal cortex should affect executive functions. For example, reduced metabolic activity in the frontal cortex is correlated with poorer performance on executive function tasks among Parkinson's patients without diagnosed dementia (Huang et al., [2007](#)). Moreover, treatment with dopamine agonists appears to help at least some cognitive symptoms of Parkinson's disease, particularly those associated with executive function and attention (Kehagia et al., [2010](#)).

However, deficient dopamine may not necessarily explain all of the cognitive symptoms seen in Parkinson's disease. For example, not everyone with Parkinson's disease (defined by motor symptoms) develops dementia, even though they all have insufficient dopamine. In addition, dopamine agonist drugs do not appear to improve memory deficits seen in some Parkinson's patients (Kehagia et al., [2010](#)). For these reasons, researchers are debating which biological mechanisms contribute specifically to dementia in Parkinson's disease (Irwin et al., [2013](#); Svenningsson et al., [2012](#)). Some researchers argue that dementia occurs when the typical dopamine deficits of Parkinson's are combined with pathology typical of Alzheimer's disease, namely, amyloid plaques and neurofibrillary tangles. Others argue that the presence in the cortex of so-called Lewy bodies, which are clumps of abnormal proteins inside cells, can account for cognitive decline (see [Figure 16.9](#)). Yet another point of view, which encompasses all of these mechanisms, is that dopaminergic deficits account for cognitive difficulties in executive function and attention that can be seen even in the absence of dementia, whereas Alzheimer-type pathology and the presence of Lewy bodies increases the risk for additional widespread dementia that includes memory impairment (Kehagia et al., [2010](#)). Future research is needed to distinguish among these possibilities.

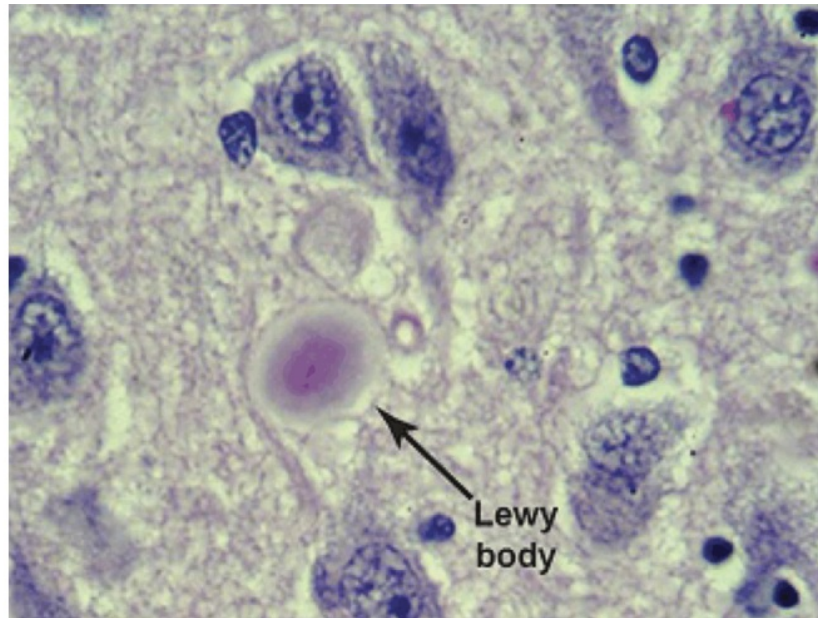


Figure 16.9 Lewy bodies in Parkinson's disease.

Lewy bodies are clumps of abnormal proteins inside neurons, and their presence is associated with dementia. They are sometimes, but not always, observed in postmortem examination of the brains of individuals with Parkinson's disease.

(from <http://lewybody.org/sites/images/lbslewybody331x249.jpg>)

While we know that Parkinson's disease is caused by destruction of midbrain dopaminergic regions (specifically, the substantia nigra), it is not clear what factors lead to that destruction. Genetics can certainly play a role: first-degree relatives of individuals with Parkinson's are between 2 and 10 times more likely to get the disease than individuals with no affected relatives; and siblings are likely to get the disorder at a similar age. Although progress is being made in identifying genes that confer risk of developing Parkinson's disease, it is unknown whether the same genes that contribute to the onset of the disorder also contribute to the development of dementia-like symptoms associated with the disorder (Svenningsson et al., [2012](#)). From the environmental side, meta-analyses suggest that an increased risk for Parkinson's has been associated with a number of potential factors, which include, in decreasing order of influence, exposure to pesticides or herbicides, head trauma, rural or farming environment, an agricultural occupation, and drinking well water (Noyce et al., [2012](#)). However, most cases of

Parkinson's disease are idiopathic, meaning that the cause of the substantia nigra deterioration is unknown.

The standard treatment for Parkinson's has been to try to offset the dopamine deficiency by giving patients L-dopa, a precursor to dopamine that can cross the blood-brain barrier. Unfortunately, it is associated with dyskinesias in about 35% of patients and with hallucinations in other patients, and there is a loss of drug efficacy over time. Moreover, while treatment with dopamine agonists appears to benefit some aspects of executive function, it can also lead to impairment in other functions, such as inhibitory control of behavior, resulting in increases in impulsiveness both on laboratory tasks and in daily life. Patients with Parkinson's who are being treated with such medications, for example, may start to gamble without concern for the financial costs that may be incurred. One possible explanation, referred to as the "dopamine overdose hypothesis," is that the increase in dopamine production triggered by medications for Parkinson's diseases is beneficial for motor functions and some dorsolateral frontal functions but at the same time creates an excess of dopamine in the ventral striatum, leading to failures of inhibitory control (Dirnberger and Jahanshahi, [2013](#)).

When a patient becomes resistant to L-dopa and the symptoms are extremely problematic, more invasive treatment options may be considered, such as ablation of the thalamus or the internal portion of the globus pallidus, or deep brain stimulation of these structures via an implanted electrode (e.g., Deuschl et al., [2006](#); Fasano et al., [2012](#)). Although these procedures are thought to improve motor functioning, controversy presently exists as to whether they have any positive cognitive consequences. Moreover, in some cases, negative effects of deep brain stimulation on cognitive and emotional functions have been documented (e.g., Fasano et al., [2012](#); Nassery et al., [2016](#)). A final therapeutic avenue is the prospect of using stem cells to replace neurons that are lost in the substantia nigra. Although such therapeutic interventions have been used for over a decade, the procedure is performed so rarely that this intervention is still in the

exploratory stages. Moreover, the focus of this research has typically been on establishing physiologically effective grafts rather than on evaluating cognitive function, so their potential benefits for Parkinson's dementia are generally unknown (see Ali et al., [2014](#); Lindvall and Kokaia, [2009](#); Politis and Lindvall, [2012](#), for reviews).

Huntington's Disease

As discussed in [Chapter 4](#), Huntington's disease is an inherited, progressive neurological disease that generally first manifests around age 35–45 and inevitably leads to death about 15 years later (for reviews, see Novak and Tabrizi, [2010](#); Ross et al., [2014](#)). The incidence of this disease is about 5–10 cases per 100,000 people. The disease begins with abnormal protein folding, due to a known genetic mutation, and ultimately destroys GABAergic (and cholinergic) neurons in the striatum (caudate nucleus and putamen) and to some degree in the globus pallidus. This destruction produces a movement disorder characterized by jerky, rapid, and uncontrollable movements (i.e., choreiform movements or chorea). [Figure 16.10](#) illustrates the loss of tissue in the basal ganglia in Huntington's disease.

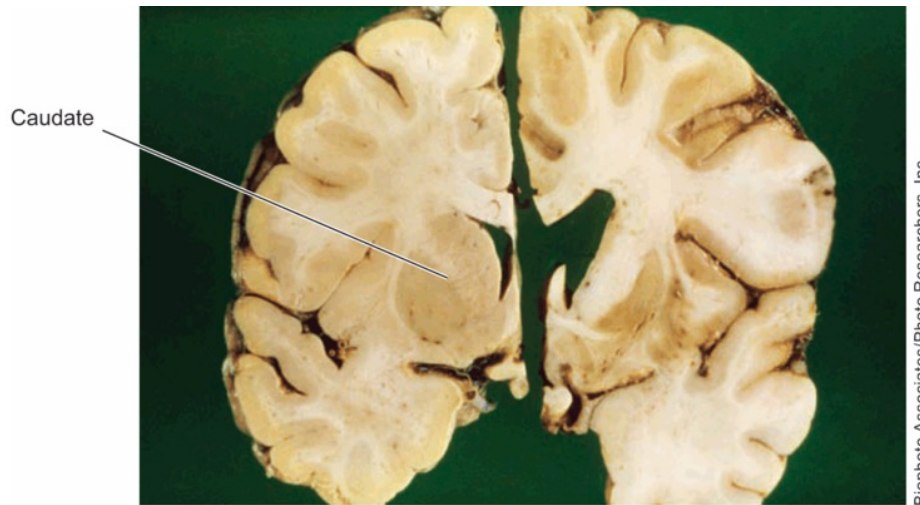


Figure 16.10 Neurological degeneration in Huntington's disease.

The caudate nucleus is much smaller in a patient with Huntington's disease (right side of image) compared to a normal person (left side of image). The ventricles are enlarged in the Huntington's patient because of lost tissue in the basal ganglia.

Source: Biophoto Associates/Photo Researchers, Inc.

While the decline in cognitive functioning in individuals with Huntington's disease approximately parallels the decline in motor functioning, with practically all patients eventually becoming demented (Jacobs et al., [2006](#); Ross et al., [2014](#)), some cognitive symptoms may be present at least 15 years before formal diagnosis by motor symptoms (Paulsen et al., [2008](#); Paulsen, [2011](#)). Huntington's patients have difficulty with executive aspects of attention, processing of spatial information, and retrieval of information from memory, as discussed in more detail below. The foregoing symptoms are often accompanied by disorganized speech and changes in personality and emotional functioning. As with other subcortical dementias, profound aphasia and apraxia are rare, a factor that allows clinicians to easily differentiate between Alzheimer's disease (or other cortical dementias) and Huntington's disease (or other subcortical dementias).

[Figure 16.11](#) illustrates the timing of symptom development in Huntington's disease. The figure shows both the early age of onset of the disease and the emergence of symptoms across motor and cognitive domains. The figure also illustrates the concept of a **prodromal** stage of the disease, which refers to a stage in which the disease has not

yet been diagnosed, but subtle symptoms are detectable in both motor and cognitive functioning among genetic carriers of the disease (e.g., Duff et al., [2010](#); Solomon et al., [2008](#); Stout et al., [2011](#)).

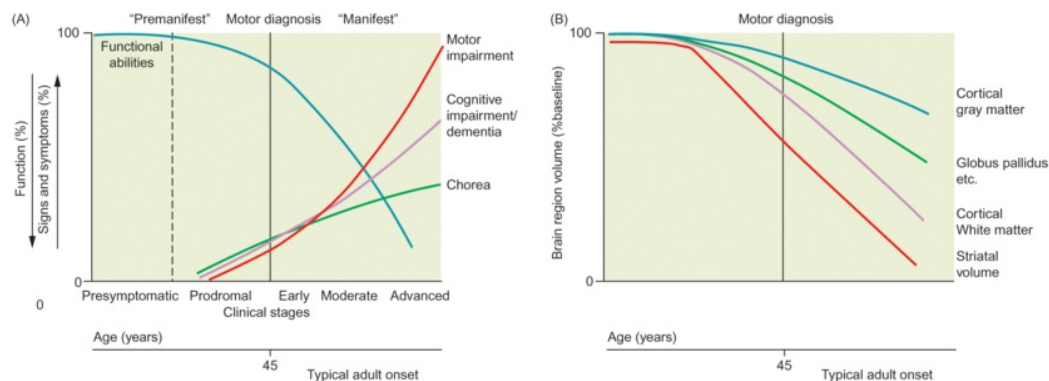


Figure 16.11 Typical time course of symptom development in Huntington's disease.

Panel A depicts emergence of symptoms. Separate lines illustrate the time course of chorea (shown in green), which refers to the characteristic jerky movements of the disorder; other motor impairment (e.g., difficulties in balance, rigidity) (shown in red); and dementia (shown in purple). Notice that these symptoms manifest themselves in the prodromal stage before a definitive diagnosis is made. Panel B illustrates decline in brain volume across cortical and subcortical regions over time relative to baseline in younger years. Once again notice that volume decreases are typically underway prior to a formal diagnosis based on motor deficits.

(from Ross et al., [2014](#))

One broad domain of cognitive dysfunction observed in Huntington's disease is in the realm of executive control and other abilities mediated by the frontal lobe. Patients with Huntington's disease have specific difficulties in initiating behavior, selecting a response, selecting a stimulus on the basis of particular attributes, and switching mental sets. In addition, they have reduced verbal fluency, perseverative tendencies, and a loss of cognitive flexibility. Such deficits are manifest on tasks such as the Wisconsin Card Sorting Test and the Stroop test. The existence of such deficits is not surprising if you

consider that the head of the caudate nucleus, which is damaged by Huntington's disease, receives much input from the dorsolateral and orbital frontal cortex. The disintegration of the connections between the frontal lobe and the basal ganglia manifests early in the course of the disease. One of the most common early complaints of individuals with Huntington's disease is that they have difficulty planning their activities and scheduling their lives.

Another domain in which patients with Huntington's disease often exhibit problems involves certain aspects of memory. The memory disorder is characterized by two main features, each of which distinguishes it from the memory problems observed in patients with Alzheimer's disease. The first main feature of memory dysfunction in patients with Huntington's disease is that they are much better at recognition than at recall. In contrast, patients with Alzheimer's disease are equally impaired at both. These findings suggest that although patients with Huntington's disease can store new information, they have difficulty making the kind of self-guided search through memory that is required to recall (rather than recognize) information. However, they are able to retrieve information when given cues, such as those provided in multiple-choice recognition memory tasks; this indicates that the information has indeed been successfully stored in memory.

Besides being affected cognitively, most individuals with Huntington's disease manifest changes in emotional functioning. About half of all patients with this disease have major depressive episodes or exhibit a depressed mood (e.g., Paulsen et al., [2005](#)). The depression often precedes motor symptoms (e.g., Julien et al., [2007](#)) and is similar to that observed in individuals with Parkinson's disease. Depression in Huntington's patients, as well as in gene carriers who have not yet been diagnosed, may be due to both the physiological effects of the disease and the knowledge of having an incurable degenerative disorder while still relatively young. Patients with Huntington's disease may also be irritable, apathetic, impulsive, aggressive, and emotionally labile. At times they even exhibit psychotic symptoms such as delusions (e.g., thinking they are

being persecuted by the FBI or that they are Napoleon reincarnated). Hallucinations (e.g., hearing voices) are more rare. These patients often act in socially inappropriate ways that are reminiscent of the behavior of patients with frontal lobe damage, and they have difficulty recognizing emotions in others (e.g., Henley et al., [2012](#)). Finally, they may often show a lack of awareness of their own deficits across cognitive and emotional domains (Hoth et al., [2007](#)).

Huntington's disease is classified as a subcortical dementia because it is caused by changes to the striatum, as discussed in [Chapter 4](#). However, Huntington's disease is also associated with changes in the cortex itself, such as cortical thinning, and such cortical changes can predict symptom severity (Montoya et al., [2006](#); Rosas et al., [2008](#)). In addition, neuroimaging studies have found Huntington's-related decreases in functional connectivity between cortical regions, such as decreased synchrony between frontal and parietal regions during a working memory task (Georgiou-Karistianis et al., [2012](#)). Such results remind us that, unlike the focal lesions that we discussed earlier in the book, degenerative diseases affect large portions of the brain.

Because the gene for Huntington's disease is known, it is possible to identify people who will develop the disease but have not yet done so. People who carry the Huntington's gene, but who are asymptomatic with regard to motor signs, exhibit poorer performance than noncarriers on tasks of memory and executive functioning (Papp et al., [2011](#); Wahlin et al., [2007](#)). People who are carriers of the gene for Huntington's disease (yet still asymptomatic) show disrupted functional connectivity between cortical regions (such as premotor regions of the frontal lobe) and the striatum (Unschuld et al., [2012](#)). Thus, Huntington's disease appears to have a deleterious effect on the brain even before the onset of motor symptoms.

There is no cure for Huntington's disease, so the aim of treatment is generally to address the motor and psychiatric symptoms. As with Parkinson's disease, there is interest in determining whether novel cellular treatments can ultimately yield new treatment options (Antoniades and Watts, [2013](#)). For example, implantation of neural

tissue or stem cells could slow or reverse the progression of the disease. In one study, researchers implanted embryonic tissue in the striatum of five patients with Huntington's disease, and found that three of the five showed cognitive improvements for the first two years after implantation; by four to six years after the surgery, these patients continued to show stabilized performance on untimed cognitive tasks, although performance decreased on timed tasks (Bachoud-Lévi et al., [2006](#)). Other potentially promising therapies attempt to stimulate or enhance the brain's natural processes of neurogenesis and neural repair (Antoniades and Watts, [2013](#)). Whether such therapies will ultimately be beneficial for treating Huntington's disease remains to be further investigated.

Mixed-Variety Dementias

Mixed-variety dementias are characterized by a substantial degree of both cortical and subcortical damage, which makes the clinical profile of these disorders an amalgam of the cortical and subcortical dementias. At present, our ability to clearly characterize the features of mixed-variety dementia is not as good as for the other types of dementia we discussed. One reason for this murkiness is that the mixed-variety dementias affect the nervous system in a heterogeneous manner.

[Vascular dementia](#), also sometimes known as multi-infarct dementia, is a common form of mixed-variety dementia and the second most common type of dementia overall (after Alzheimer's disease) (for reviews, see O'Brien and Thomas, [2015](#); Venkat et al., [2015](#)). Vascular dementia results from the cumulative effects of many small strokes that tend to create both cortical and subcortical lesions. Thus, unlike a single stroke, which tends to compromise a specific mental capacity (e.g., speech output), vascular dementia affects multiple areas over time as the consequences of multiple small strokes accumulate. In addition, in vascular dementia, the regions of the circulatory system that fail may vary from person to person, leading to heterogeneity across patients. In some cases, the vascular damage is mainly cortical, more often in the frontal lobes than in other lobes of the cortex. In other cases, especially in individuals with arterial

hypertension (high blood pressure), lesions occur in the small blood vessels supplying subcortical areas, primarily those in the basal ganglia, internal capsule, thalamus, and pons.

The presentation of patients with vascular dementia is often similar to that of patients with Alzheimer's disease (Mathias and Burke, [2009](#)). Ways to distinguish between the two include the patient's medical history, brain imaging, and neuropsychological testing. Evidence for a vascular contribution to dementia comes from a long-standing medical history of arterial hypertension, focal neurological signs that suggest a stroke (such as weakness of an extremity), and MRI or PET scans revealing specific and multiple infarcts of the cortex in either the white or gray matter (see [Figure 16.12](#)).

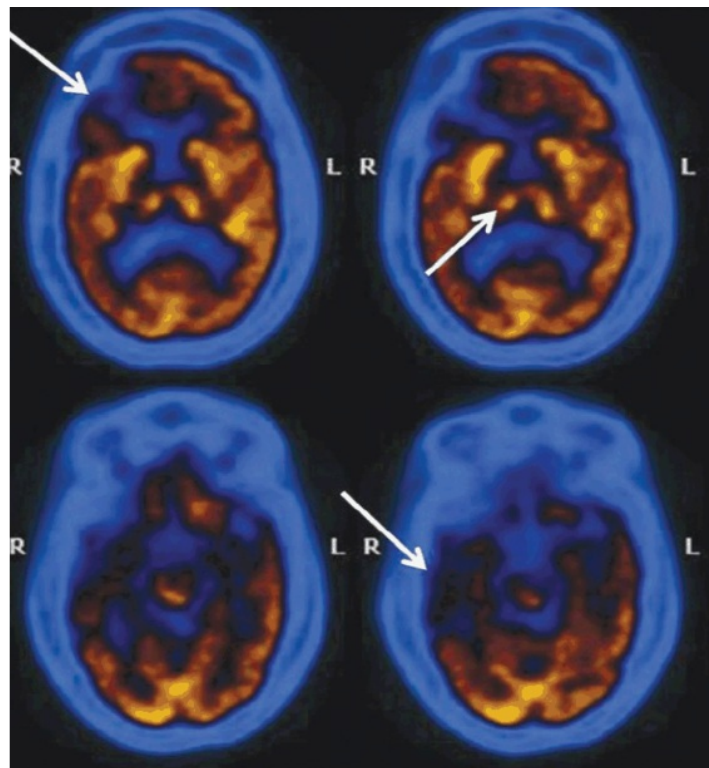


Figure 16.12 Example illustrating lesions associated with vascular dementia.

This figure shows the brain of a patient with vascular dementia, scanned with PET imaging. Arrows point to areas of hypoperfusion, that is, reduced perfusion due to the vascular lesions.

(from Sharma et al., [2011](#))

Vascular dementia and Alzheimer's disease can also be distinguished on the basis of their time course. Typically, vascular dementia occurs with a relatively abrupt onset (due to a stroke), is accompanied by a stepwise rather than gradual course (because the effects are compounded by each additional stroke), and is not restricted to onset in the later years. This pattern contrasts with the pattern observed in Alzheimer's disease, which tends to occur later in life and has an insidious onset, slow progression, and an unremittingly downward course. Finally, because vascular dementia is associated with stroke, the pattern of impairment can fluctuate, being worse initially and then improving. Moreover, treatment of hypertension may help prevent further progression of the disease, whereas hypertension is not a factor that characterizes or influences Alzheimer's disease.

In terms of their neuropsychological profile, patients with vascular dementia usually demonstrate the same type of pattern observed in patients with Alzheimer's disease. For this reason, it is difficult to distinguish the two disorders definitively based on cognitive functioning alone (Mathias and Burke, [2009](#)). Patients with vascular dementia are somewhat more likely to exhibit deficits on tasks relying on frontal lobe function and to display a pattern suggestive of subcortical involvement. For example, patients with vascular dementia and Alzheimer's disease usually perform similarly on tests assessing visuospatial ability, language, and memory, but patients with vascular dementia usually perform more poorly on tests measuring executive function, verbal fluency, and attention, all of which are believed to rely on the frontal lobes. Consistent with the idea of greater subcortical involvement in vascular dementia than in Alzheimer's disease, patients with vascular dementia tend to exhibit slowing of performance on motor tasks and, to a lesser degree, on cognitive tasks in general.

While vascular dementia and Alzheimer's disease can be distinguished, it is also not uncommon for them to occur together, complicating diagnosis (Schneider et al., [2007](#)). The co-occurrence of these two conditions may simply reflect the presence of two independent disease trajectories associated with aging (e.g., Launer et al., [2008](#)).

Alternatively, the vascular changes associated with multiple mini-strokes may contribute in some way to the pathology that becomes manifest as Alzheimer's disease (Iadecola, [2013](#)). In either case, the phenomenon of vascular dementia reminds us of the importance of cardiovascular health for cognitive functioning, particularly later in life.

Multiple Sclerosis

One of the most common neurological diseases of nontraumatic origin, [multiple sclerosis \(MS\)](#), affects the cognitive functioning of young and middle-aged adults (see Kamm et al., [2014](#), for review). MS is characterized by multiple discrete areas of scarring (sclerosis), ranging in size from 1 millimeter to several centimeters, in which neurons have absent or damaged myelin (see [Figure 16.13](#)). The destruction of myelin in MS is traditionally thought to result from an immunological disruption in which the body incorrectly identifies part of its own system as a foreign agent or invader and attacks it (i.e., an autoimmune disorder). However, other researchers argue that the death of oligodendrocytes, which form myelin, may precede the autoimmune response rather than resulting from it (for discussion, see Matute and Pérez-Cerdá, [2005](#); Trapp and Nave, [2008](#)). In either scenario, demyelination leads to axonal degeneration and interferes with neural transmission. The sites affected tend to be diffuse and multifocal, occurring in both the central and peripheral nervous system. However, certain sites, such as those in the periventricular regions (peri, “near”; ventricular, “having to do with the ventricles”) tend to be more affected. Although MS is generally considered to be a disease of the brain's white-matter tracts, gray matter may also be lost in the disease (e.g., Inglese et al., [2004](#); Rocca et al., [2015](#); Rovaris et al., [2006](#)). Losses of both gray and white matter have been associated with cognitive dysfunction (e.g., Sbardella et al., [2013](#)).

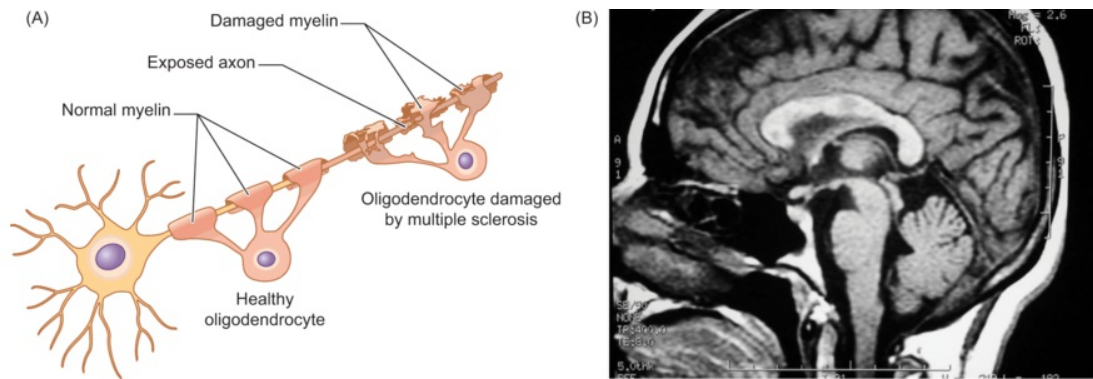


Figure 16.13 Damage to myelin in multiple sclerosis.

When the myelin is damaged, transmission of the action potential along the axon is impaired (panel A). The resulting lesions to white-matter tracts, such as the corpus callosum, can be seen on MRI scans (panel B).

MS occurs in approximately 85 of every 100,000 individuals, affecting women about twice as often as men (Alonso and Hernán, [2008](#); Noonan et al., [2002](#)). Its etiology is unknown, although evidence suggests both environmental and genetic contributions. Interestingly, MS is linked to geographical locale: it is less prevalent near the equator and more prevalent toward the geographic poles. Explanations for this geographical association include the possibility that the causative agent may be a slow virus that is more common in temperate and colder locales or the possibility that vitamin D from the sun acts as a protective factor in more equatorial regions (e.g., Kamm et al., [2014](#)). Prior exposure to infectious mononucleosis or the Epstein-Barr virus, as well as a history of smoking, have also been associated with increased risk for MS (Belbasis et al., [2015](#)).

A genetic risk for the disease is implied by findings that one in five patients with MS have a family member with the disease. In addition, a higher concordance rate (20–30%) occurs in monozygotic twins (who share identical genetic material) than in dizygotic twins (2–5%) (who have only half their genetic endowment in common). MS is associated with genes that influence the body's immunologic response, most notably the human leukocyte antigen (HLA) gene on the short arm of chromosome 6 (Gourraud et al., [2012](#); Oksenberg et al., [2008](#)). However, researchers agree that MS is not a single-

gene disorder, but rather involves interactions between numerous genetic and environmental factors.

Because of the diffuse nature of the lesions in MS and the variability of their location, MS has multiple manifestations. The exact symptoms depend on the sites in the nervous system where myelin is damaged. Initial symptoms often involve weakness in the extremities or difficulty in some aspect of sensory processing. Sensory and motor tracts are especially susceptible to MS, because they are often myelinated to allow speedy transfer of information along the long distances from the peripheral receptor to the brain or from the brain to the muscle. For the person affected, the first manifestations of the disease can be petrifying. Common initial symptoms include a blurring or loss of vision, persistent tingling or numbness of a body part, weakness of a body part, or difficulty in coordination.

Unlike many of the other syndromes we have discussed in this chapter, the course of MS is highly variable (see [Figure 16.14](#)). A person can have an acute flare-up that results in a hemianopsia, only to have the hemianopsia dissipate and remit – but a subsequent attack could then leave the person with a permanent visual loss. Because MS usually affects people in the prime of their lives and its progression is highly unpredictable, the disease is extremely stressful for those who have it, as well as for their families. A person afflicted with MS never knows whether he or she will have the next attack 20 years later or if a series of exacerbations will lead to permanent blindness or paralysis in the near future.

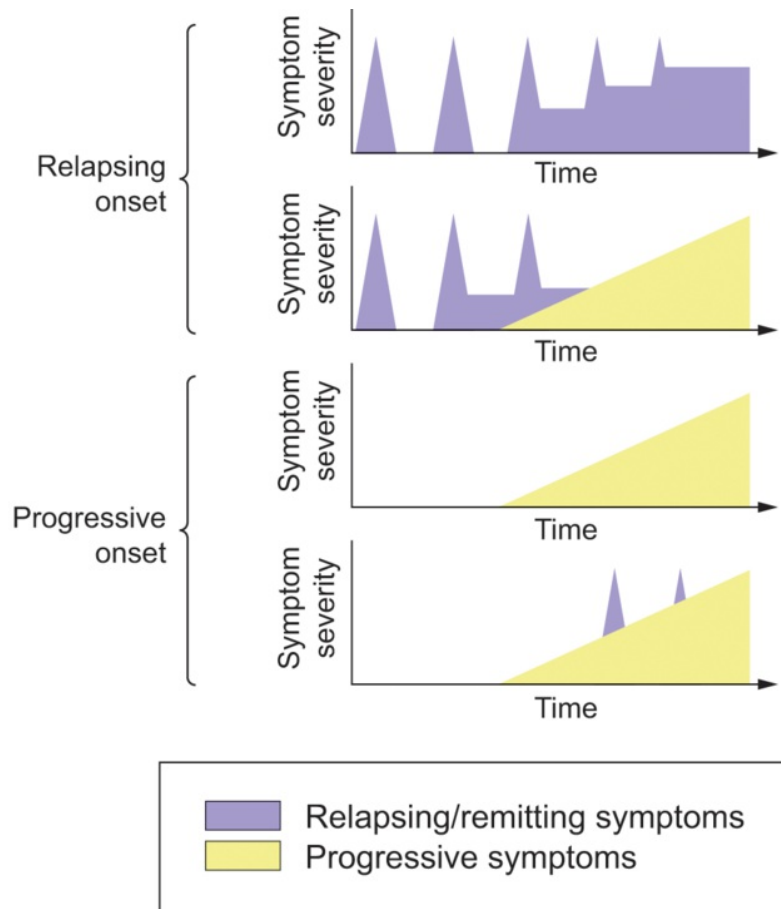


Figure 16.14 Varied time courses of multiple sclerosis (MS).

MS can exhibit a relapsing–remitting pattern, in which symptoms appear and then disappear (shown by the “peaks” in the figure), or it can have a progressive pattern, in which symptoms slowly get worse over time (shown by the “ramps” in the figure). Combinations of a relapsing–remitting pattern and progressive MS are also possible. The top two panels illustrate MS with a relapsing–remitting pattern onset, although progressive changes can also occur subsequently, as shown in the second panel. In the bottom two panels, the onset of the disease displays a progressive pattern, although symptom peaks may be superimposed upon that.

(from Kamm et al., [2014](#))

Some people with MS exhibit little if any cognitive disability, whereas others clearly show cognitive compromise. Researchers have estimated that cognitive deficits occur in 40–60% of all MS patients (for review, see Rocca et al., [2015](#)). The degree of cognitive impairment predicts how effectively the patient is able to carry out everyday

tasks of life (Kalmar et al., [2008](#)). When cognitive difficulties do occur, they tend to be variable and do not affect as large a range of function as observed in patients with dementia. If a typical pattern of cognitive disability exists in MS, it involves slowed information processing and difficulty in memory and conceptual reasoning along with a general sparing of language and knowledge systems (Chiaravalloti and DeLuca, [2008](#); Rocca et al., [2015](#)). On memory tasks, people with MS have difficulty recalling information but display good recognition memory, which suggests an impairment of the ability to guide a search through memory. Patients with MS also have difficulty on tasks that require conceptual abstraction, and they may exhibit deficits on visuospatial tasks. However, many of these tasks rely on either speeded performance or manual dexterity, making it difficult to determine the degree to which the deficits are due to peripheral sensory or motor problems or to assess whether they reflect central cognitive problems. The pattern of neuropsychological difficulties suggests a disruption of processing involving both subcortical structures (such as the thalamus and the basal ganglia) and the cortex, mainly the frontal lobes, as well as the connections between these regions.

The cognitive changes in MS are usually accompanied by changes in mood and personality. The most common disorder in MS is depression, occurring in 30–60% of all affected individuals (Siegert and Abernethy, [2005](#)). These mood changes could be normal reactions to having a debilitating, unpredictable, chronic disease, or they could reflect the fatigue that is often associated with the disorder. Mood changes also may, in part, reflect some of the organic changes that accompany the disease. Research has found that cognitive-behavioral therapy can be beneficial for treating MS-related depression (Hind et al., [2014](#)).

Over time, cognitive skills of patients with MS may either continue to deteriorate or may be maintained. Once again, we see that the course of the disease varies widely from one person to the next. In one longitudinal study of approximately 100 patients with progressive MS, cognitive function declined over a period of two years for approximately one-third of the sample and remained stable or even improved in the other two-thirds (Camp et al., [2005](#)). Interestingly, changes in MRI measurements did

not predict changes in cognitive function, but better cognitive performance at the beginning of the study predicted a greater likelihood of maintaining cognitive function over the two years. Thus, initial cognitive performance was a better predictor of the course of the disease than the MRI variables (which included brain volume and the amount of white-matter lesions).

Because MS affects myelination of axons, it is logical to suspect that communication between brain regions may be disrupted. Indeed, numerous studies have now investigated functional connectivity, meaning co-activation of interconnected brain regions, in MS patients either in a resting state or while performing cognitive tasks (Filippi et al., [2013](#); Schoonheim et al., [2015](#)). Although many studies have found alterations in functional connectivity in MS, the studies differ in the direction of the disruption: some studies found decreased functional connectivity, and some found increased functional connectivity. Likewise, when making comparisons within a set of patients with MS, some studies have found that increased functional connectivity in MS is associated with better cognitive function, and other studies have found it is associated with worse cognitive function. Researchers speculate that the increase in co-activation between brain regions sometimes seen in MS may actually reflect a compensatory process of some sort, the brain's way of attempting to maintain functionality even with damaged connections between brain areas. As with many clinical conditions, it can be difficult to disentangle the direct effects of the disease process from the brain's attempts to adapt to that disease presence.

No cure exists yet for MS; what exists instead are “disease-modifying treatments” that attempt to curtail symptoms and delay relapses (Castro-Borrero et al., [2012](#); Wingerchuk and Carter, [2014](#)). Currently, a drug known as interferon beta-1b is considered the main line of treatment. Interferons are proteins produced by the body that have antiviral characteristics and modulate the immune response. Unlike other therapies, which just stayed the course of the disease, interferon appears to actually reduce exacerbations of the disease and can have at least some modest benefits on

cognition (Amato et al., [2013](#)). For example, over a period of a year or more, interferon beta-1b had a beneficial effect on cognitive performance for individuals with a relapsing-remitting, rather than continually progressive, form of MS. In particular, the drug aided visual memory, learning, problem solving, and complex attentional control, skills that tend to decline over a similar time period in individuals who do not receive such medication (Barak and Achiron, [2000](#); Fischer et al., [2000](#)). Some researchers have proposed giving interferon to people who have symptoms that are suggestive but not definitive of MS, because it may prevent the onset of the full disorder (Comi, [2009](#)).

Ultimately, researchers are aiming for treatments that will do more than just limit the degree of future cell loss; they would like to be able to repair the damage to cells so as to help patients recover lost functions. Potential strategies include promoting axonal regeneration and promoting myelin repair (e.g., Deshmukh et al., [2013](#)). Stem cells may prove to be especially beneficial in repairing myelin (Connick et al., [2012](#); Rice et al., [2013](#)). However, most of these research directions are still in the exploratory stages, and it is not known how any such therapies would affect sensory, motor, or cognitive symptoms of the disorder.

Epilepsy

Throughout much of history, epilepsy has had a negative connotation; epileptic seizures have been referred to as “fits,” and people with epilepsy have been stigmatized. We now know that such characterizations are unfair and that epilepsy is a neurological problem that has nothing to do with the person’s character. [Epilepsy](#) is a disease in which seizure activity is recurrent but intermittent. Emphasizing the recurrent nature, a diagnosis of epilepsy is based on the presence of two or more seizure occurrences. [Epileptic seizures](#) are episodes in which synchronous activity of nerve cells increases so that a gigantic hyperpolarization of neurons spreads over a large area in an atypical and abnormal manner.

Seizures come in many varieties, and approaches to categorizing them have changed over the years (Stafstrom and Carmant, 2015). Currently, seizures are divided into two major classes (see [Figure 16.15](#)). One major class is generalized-onset seizures, so called because they involve abnormal activity in large networks on both sides of the brain at the time of onset. This contrasts with focal-onset seizures, in which the abnormal activity starts in a particular region on one side of the brain. Focal-onset seizures may remain fairly localized, or they may then spread to other brain regions. Sometimes seizures may be classified as unknown onset until more information can be gathered about whether the onset is generalized or focal.

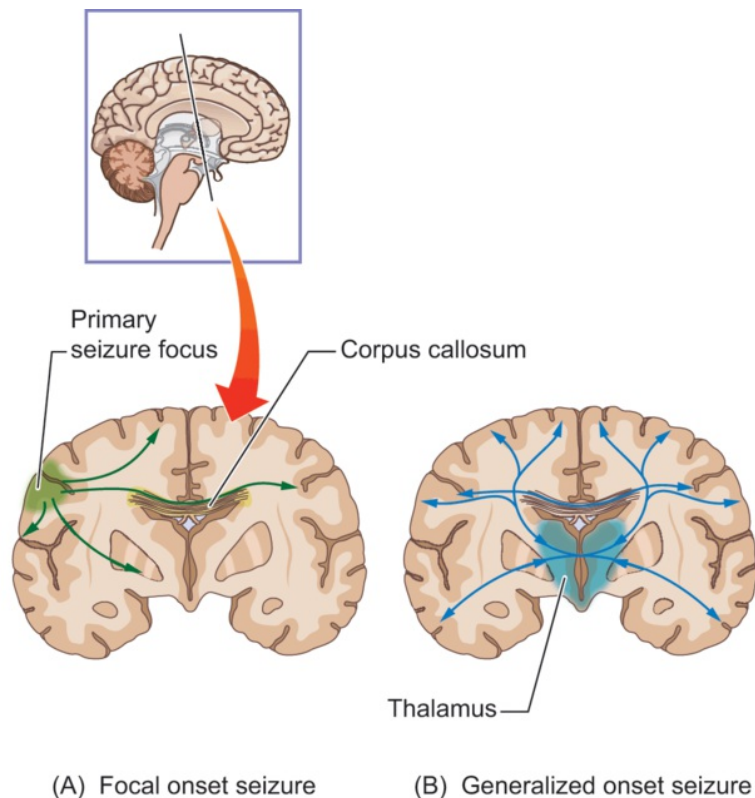


Figure 16.15 Seizures spread throughout the brain.

The abnormal electrical activity generated from a partial (focal) seizure (A) or a generalized seizure (B) can spread rapidly through the brain over fiber pathways.

Additional subtypes of seizures are categorized by the person's level of awareness during the seizure and by the kinds of behavior that are exhibited. Some seizures, called absence seizures, involve brief periods of "blanking out" or altered awareness. Other

kinds of seizures, called tonic-clonic seizures, involve convulsive behavior due to changes in muscle activity, such as stiffness (tonic changes) and jerkiness (clonic movements). Yet other seizures involve changes in breathing, thinking, speech, emotions, or sensations, including numbness or tingling. Because they involve abnormal electrical activity, different types of seizures are identifiable by characteristic abnormalities in the EEG (see [Figure 16.16](#)).

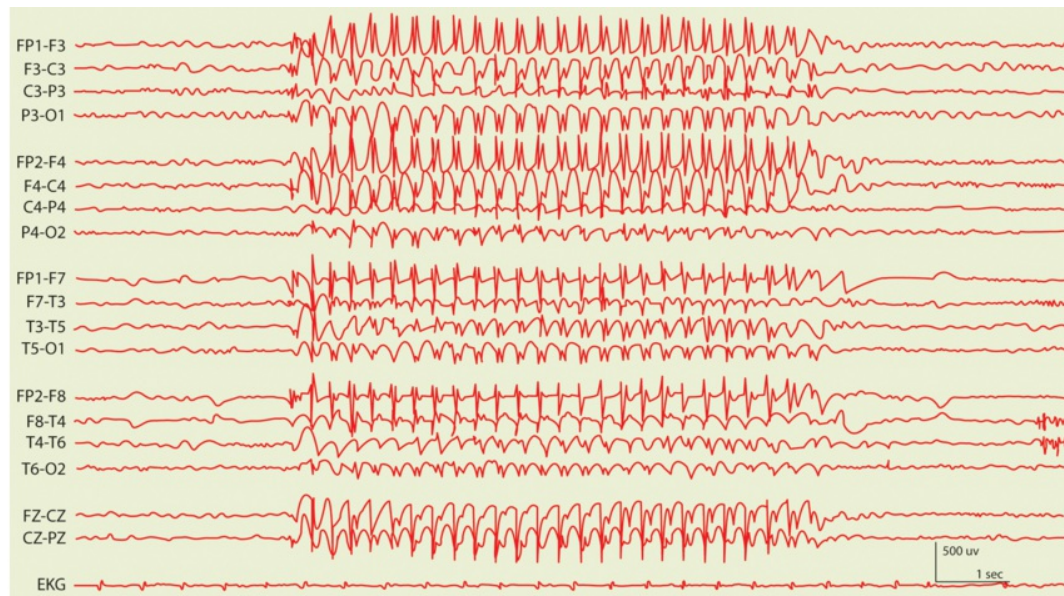


Figure 16.16 Seizure disorders are detectable by characteristic patterns in the EEG.

This example shows the EEG pattern during an absence seizure in childhood. The different traces depict EEG activity at different scalp sites (e.g., FP1, etc.) during the seizure.

Sometimes the cause of a seizure disorder is known, and then the seizure disorder is termed symptomatic. Typical causes include head trauma, metabolic disorders, infection, toxins, and tumors. For example, approximately 20% of all people who sustain a penetrating brain injury develop epilepsy. In contrast, seizure disorders with no known cause are called idiopathic. For both symptomatic and idiopathic types of epilepsy, individual seizure episodes can be triggered by a variety of stimuli, with the likely trigger varying from person to person. It often takes an affected person some time

to determine exactly what the exacerbating stimulus is. Seizures may be triggered by certain sensory stimuli, such as flashing lights; particular sounds; reading or laughing; certain classes of drugs, including alcohol; specific foods; and hormonal changes, such as those associated with puberty. Stressful situations, especially those induced by sleep deprivation, can lead to seizure activity (e.g., Ferlisi and Shorvon, [2014](#)). In fact, so potent is sleep deprivation in bringing on seizure activity that neurologists will evaluate the likelihood of a diagnosis of epilepsy by recording an individual's EEG after he or she has gone without a night's sleep (e.g., Derry and Duncan, [2013](#); Parisi et al., [2010](#)). Once triggers are identified, the person will try to avoid the situation or stimulus that leads to a seizure.

Epilepsy is associated with impaired cognitive and psychosocial functioning in many cases. Clearly, consciousness is disrupted during the seizure and this disruption impairs cognition, but interictal (i.e., between-seizure) consequences occur as well. For example, in the interictal state, the connectivity between brain regions and networks is altered in people with epilepsy compared to controls; moreover, the degree of disruption is associated with disease duration and seizure frequency (Liu et al., [2017](#)). Some cognitive deficits in the interictal period likely reflect dysfunction of the area from where the seizure originates, such as the memory problems and word-finding difficulties associated with temporal lobe seizures. Other difficulties are more generalized. These include poor sustained attention, compromised executive function, and lengthening of reaction time. Cognitive difficulties associated with epilepsy are especially important to recognize in pediatric cases, as they may affect performance in school for children afflicted (for review, see Nickels et al., [2016](#)). For example, one study found that children with active epilepsy had a higher-than-expected rate of co-occurring attention-deficit/hyperactivity disorder, autism spectrum disorder, or low intellectual functioning (Reilly et al., [2014](#)).

Epilepsy is sometimes associated with psychiatric disorders that occur postictally or chronically. For example, one study found that people with epilepsy had an eight-fold increase in risk for psychosis, compared to the general population (Clancy et al., [2014](#)).

People with epilepsy may show psychotic features similar to those observed in schizophrenics, except that they retain interpersonal skills and appropriate emotional affect. Other commonly observed psychiatric symptoms are anxiety and depression (Hoppe and Elger, [2011](#)). People with temporal lobe epilepsy may also exhibit an odd constellation of personality traits interictally. The characteristics of this syndrome are an interpersonal “stickiness,” in which the person doesn’t know when to disengage from interaction with someone else; empty, verbose, and pedantic speech; a preoccupation with religious concepts, though not usually of an organized nature; and excessive writing, such as excessive note-taking or writing in diaries. The existence of such a syndrome, however, is controversial (Foran et al., [2013](#); Mula, [2013](#)).

The two main forms of therapy for epilepsy are drug therapy and surgery. The first step in any treatment involves the administration of anticonvulsant medication, which reduces the likelihood of epileptic discharges. Fortunately, drug treatment can be very effective for many people with epilepsy (for review, see Schmidt and Schachter, [2014](#)). Three major classes of drugs are used. One class, which includes barbiturates (such as phenobarbital), mimics the neurotransmitter GABA, or potentiates its transmission. GABA is the main inhibitory neurotransmitter in the brain, as we learned in [Chapter 1](#). Another class of anticonvulsants, which are known as hydantoins, and includes phenytoin (Dilantin) and carbamazepine (Tegretol), act to block the influx of sodium into the neuron, which reduces the ability of neurons to fire at high rates. More recent anti-epileptic drugs (such as lamotrigine) work by attenuating the release of glutamate, which is the main excitatory neurotransmitter in the brain (see [Chapter 1](#)). Regardless of the type of drug, the main goal of these pharmacological interventions is to reduce neuronal firing so as to preclude the seizure activity. As with all other drugs, anti-epileptic drugs can have side effects, such as excessive sedation, and when given in too large a dose can impair cognition. Therefore, drug administration must be titrated – that is, adjusted bit by bit – so that the physician can find the dosage that has the greatest efficacy against seizures with the fewest side effects on cognition.

While drug treatment is generally effective for about 70–80% of people with epilepsy, the remainder, those with drug-resistant epilepsy, are more difficult to treat. If the focal origin for the seizure is clear, the physician and the patient may opt for surgery to remove the source of the seizure activity. Although this might seem like a relatively drastic option, misfiring cells can recruit or otherwise influence healthy cells to exhibit epileptiform activity, a phenomenon known as kindling, much the way small twigs can serve to kindle larger logs to catch on fire. Removing the tissue that is the source of the seizure activity helps preclude healthy areas from becoming compromised (see Jette and Wiebe, [2013](#), for review). As discussed in the [preceding section](#), focal seizures are most often localized to temporal and frontal areas. Especially when the focus is in the temporal areas, surgical resection of epileptiform tissue may be associated with memory loss (e.g., Sherman et al., [2011](#)).

Researchers continue to search for new treatments, because medication is not effective for all patients, and because surgery is highly invasive and appropriate only for those with focal seizures. Some research has explored whether cell or gene therapies may be effective (Löscher et al., [2008](#); Roper and Steindler, [2013](#)). For example, transplantation of fetal tissue or genetically engineered cells into the hippocampus may be beneficial in reducing temporal lobe epilepsies. Another possible avenue for intervention is through external stimulation methods. For example, in a rodent model of epilepsy, researchers found that transcranial electrical stimulation could be used to inhibit a developing seizure (Berényi et al., [2012](#)). Other researchers have used optogenetic methods to disrupt developing seizures in rodents (Krook-Magnuson et al., [2013](#)). However, these avenues are still limited to investigations with animal models, and translation to humans remains uncertain.

Disorders of Conscious Awareness

When a patient suffers a very severe brain injury that results in a sustained loss of conscious awareness, family members face questions fraught with fear and anxiety:

How can we tell what the patient is thinking and feeling? Is he or she able to think or feel anything at all? In this final section, we consider the level of mental function that may be possible when a traumatic brain injury leaves a patient in a state of severely altered conscious awareness. The topic is highly controversial, not only because of scientific and philosophical challenges in defining and measuring conscious awareness, but also because of the ethical implications for compassionate treatment at the end of life. (For thoughtful reviews, see Bruno et al., [2011](#); Demertzi et al., [2013](#); Owen and Coleman, [2008](#).)

Physicians must distinguish between several different disorders of consciousness that may follow a severe brain injury. Generally, a [coma](#) is a condition in which the patient does not show any evidence of awareness or communication, does not open his eyes, and does not exhibit any kind of sleep–wake cycle. Comas typically last for a limited period of time (from a few days to a few months), and they typically resolve in one of two basic ways: the patient may die, or the patient may emerge from the coma and recover some level of functioning. For example, a patient may emerge from a coma into a vegetative state.

A vegetative state is a condition in which the patient shows no evidence of awareness or communication, but (unlike a coma) exhibits a sleep–wake cycle and has eyes open during the wakeful periods. Recently, researchers and clinicians have proposed changing the name of this condition from vegetative state to [unresponsive wakefulness syndrome \(UWS\)](#), to avoid the insensitive connotations associated with likening a person to a vegetable (Laureys et al., [2010](#)). Here we will generally use the more recent term, UWS, which can be considered synonymous with the older term, vegetative state. Patients with UWS may exhibit some simple behaviors, such as smiling, but these behaviors seem random, rather than elicited in response to external stimulation. In addition, the condition is marked by the absence of even the most basic form of communication. For example, if asked to blink twice to answer “yes” to a question, the patient will continue to stare blankly. If this state lasts more than one

month, it is referred to as persistent. The chances of emerging from a persistent UWS condition and regaining some level of conscious awareness are low, but some cases of recovery have been reported (Estraneo et al., [2010](#); Kotchoubey, [2009](#); Zeman, [1997](#)).

Unresponsive wakefulness must be distinguished from a [minimally conscious state](#), in which there are intermittent signs of awareness and purposeful action. Both of these must also be distinguished from [locked-in syndrome](#), in which cortical function and awareness are normal but a brainstem injury prevents almost all motor output. Locked-in patients are able to communicate using simple eye movements. One of the most dramatic locked-in cases is featured in the 2007 movie, *The Diving Bell and the Butterfly*, which tells the story of how the French journalist Jean-Dominique Bauby wrote his memoir after a massive stroke left him with locked-in syndrome. He did so over a period of 10 months by blinking his left eyelid. To “write,” he would view a list of letters in sequence, and when he saw the letter that he wanted, he would blink his eye. It took an estimated 200,000 blinks to write the book, and writing a single word took, on average, two minutes.

[Table 16.6](#) lists and compares different states of consciousness. It is important to be aware that there is controversy surrounding these classifications, and they may well continue to evolve in the future. As you can see in [Table 16.6](#), the key feature differentiating among minimally conscious, UWS, and locked-in patients is the degree to which responsive behavior is present. In practice, it can be very difficult for a clinician to infer a patient’s level of awareness based on behavior alone. Distinguishing between unresponsive wakefulness and the minimally conscious state is particularly difficult, because the clinician must judge whether any emitted behaviors are simple reflexes being spontaneously performed, or whether they represent consciously aware and intentional actions. The diagnosis of UWS is based on absence of evidence of responsiveness, and making decisions based on absence of evidence is always tricky from a logical standpoint because it assumes that the clinician hasn’t missed anything in her observations. Furthermore, the distinction between UWS and minimally conscious

states, while subtle and prone to misdiagnosis, can have serious ethical and legal implications.

Table 16.6 Different Types of Altered Awareness in Brain-Injured Patients

| Clinical Observation | | | |
|---|------------------|--------------|--|
| Condition | Sleep-Wake Cycle | Eyes Opening | Responsive Behavior |
| Coma | No | No | No |
| Unresponsive Wakefulness (Vegetative State) | Yes | Yes | No |
| Minimally Conscious | Yes | Yes | Intermittent |
| Locked-In Syndrome | Yes | Yes | Yes, when measured through blinks or eye movements |

In recent years, researchers have argued that functional brain imaging evidence may help doctors and families to better understand the patient's level of mental function (e.g., Bruno et al., [2011](#)). According to this view, brain imaging could allow for an inference about the patient's awareness that does not depend solely on the patient's outward behavior, which at least in theory could be compromised even if mental awareness is intact. Structural imaging findings have long been used to provide some clues. For example, if a patient's cerebral cortex is totally destroyed, it is safe to assume that little higher-level cognition is possible. Likewise, EEG can distinguish overall states of consciousness (e.g., coma versus alertness, evidence of sleep-wake cycles). In the most

severe cases, the lack of EEG activity, often referred to as “flat-lining,” is used as an indication of brain death. However, functional brain imaging has a unique ability to probe specific higher-level cognition functions in patients with disordered awareness.

One of the most dramatic fMRI studies suggested that a patient with UWS may have retained much more higher-level cognition than could have been inferred on the basis of her behavior alone (Owen et al., [2006](#)). The patient, who was classified as being in a vegetative/UWS state, was verbally instructed to perform mental imagery tasks that typically activate certain brain regions. For example, imagining a particular motor sequence such as playing tennis activates the supplementary motor area, and imagining walking around one’s house activates the parahippocampal gyrus and parietal cortex, which are important in spatial navigation. In a startling finding, the patient showed the same patterns of brain activity as did normal controls when asked to engage in such mental imagery tasks (see [Figure 16.17](#)). These findings imply that the patient understood the instructions and was able to imagine complex activities like playing tennis or walking around her house.

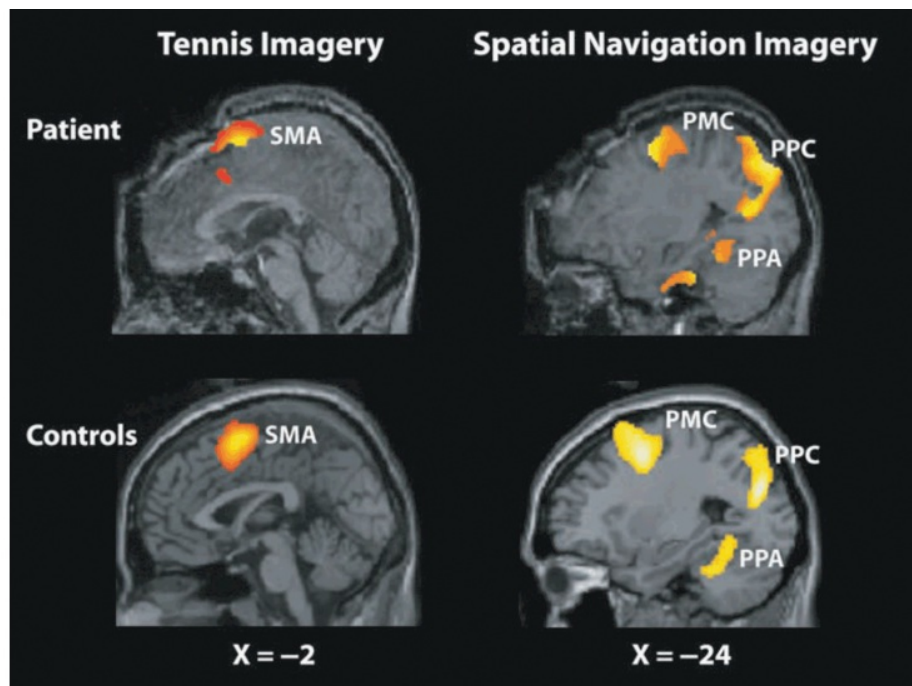


Figure 16.17 Brain activity indicates possibility of high-level cognition in vegetative states.

Participants were asked to imagine playing tennis or navigating through the rooms of their home. The brain activity generated by a patient in states of unresponsive wakefulness (top row) is highly similar to the pattern generated by neurologically normal people (bottom row). Thus, even though the patient is unable to show overt signs of awareness or intentional action in her behavior, she is able to generate some kinds of mental imagery on command. SMA = supplementary motor area; PMC = premotor cortex; PPC = posterior parietal cortex; PPA = parahippocampal place area.

Source: Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., and Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, 313, 1402. Reprinted with permission from AAAS.

Subsequent studies using fMRI and EEG methods have provided additional evidence for some degree of mental function in patients with UWS, despite the fact that they lack evidence of purposeful behavior. For example, individual patients have been shown to exhibit motor cortex activation in response to verbal commands to move

(Bekinschtein et al., [2011](#); Cruse et al., [2012](#)), activation of language areas in response to linguistic stimuli (Coleman et al., [2007](#); Di et al., [2007](#)), and activation of the right fusiform gyrus in response to familiar faces (Menon et al., [1998](#)).

These findings challenge the current system for classifying patients as “unaware” based on behavioral observations, and, as you might imagine, they have raised a host of additional questions. First, does fMRI or EEG activation in response to a task necessarily reflect “awareness”? What should be the appropriate criteria for defining someone as “consciously aware” versus “unaware”? Second, what proportion of UWS patients show evidence of higher-level cognition in brain imaging studies? Existing studies imply that it is only a small subset (e.g., Monti et al., [2010](#)). This raises questions about what characteristics – such as the type of injury, length of time in the unresponsive state, age, or other participant characteristics – differentiate between the small subset of UWS patients who show neural evidence of some, albeit relatively minimal, mental function versus the majority who don’t.

Furthermore, could brain imaging evidence be used to predict which patients have a better likelihood of emerging from unresponsive wakefulness into a minimally conscious or even fully conscious state? Recent studies indicate that both DTI and functional connectivity measures can reliably distinguish between UWS and minimally conscious patients (Fernández-Espejo et al., [2011](#); Kotchoubey et al., [2013](#); see also Stender et al., [2014](#)), so perhaps in the future such tools could be used to differentiate which UWS patients have a better prognosis for recovery.

Perhaps most difficult are the ethical issues. If a patient is behaviorally unresponsive to stimulation, seeming to stare blankly for months at a time and failing to respond in any way to others, but her brain shows evidence that she can imagine activities of daily life like playing tennis, what efforts should be made to sustain her life? UWS patients typically are able to breathe on their own, so they do not need to be on respirators, but they do need to be given food and water if they are to survive. Thus,

families are faced with wrenching decisions about end-of-life care, with limited ability to fully understand the mental states of their loved one.

Indeed, this complex issue illustrates both the promise and the limitations of cognitive neuroscience methods in addressing challenging clinical issues of the relationships between brain activity and mental function. In the next and [final chapter](#), we broaden our view of cognitive neuroscience to consider the interface between neuroscience and society, including both the potential promise for cognitive neuroscience to yield insights that benefit society, and the challenges in appropriately applying knowledge from cognitive neuroscience to address vexing societal dilemmas.

Summary

Closed Head Injury

- Closed head injury, which occurs when the head hits or is hit by a blunt object, as happens in vehicular accidents, falls, and sport-related injuries, is generally associated with changes in consciousness.
- Acute consequences of head injury include difficulties in concentration, attentional problems, and posttraumatic amnesia. Longer-term effects include difficulties with abstract thought, anxiety, depression, and anger.

Dementing Diseases

- Cortical dementias compromise a wide range of mental functions, including memory, language, spatial abilities, and object recognition.
- Alzheimer's disease, considered a cortical dementia, is prominently characterized by memory impairment, with compromise of a large variety of other cognitive functions as well.
- Alzheimer's disease is associated with specific neuroanatomical changes: the presence of neurofibrillary tangles and amyloid plaques in brain tissue that first

manifest in regions at the base of the brain and over time involve more and more brain regions.

- Drug therapies are designed to delay the effects of Alzheimer's disease, but cannot cure it. For the most part, they work on boosting the amount of acetylcholine in the nervous system.
- Frontotemporal dementia is characterized by difficulty with language and changes in emotion and personality. Unlike in Alzheimer's disease, degeneration is most prominent in frontal and temporal regions.
- Subcortical dementias are characterized by difficulty with tasks related to motor functioning, attention, and executive control, along with poor memory recall but intact recognition, and symptoms of depression.
- In Parkinson's disease, there is a general slowing of motor functioning and thinking, dysfunction of executive processes, difficulty in memory retrieval, apathy, and depression. This behavioral profile, along with damage in the basal ganglia, leads these difficulties to be classified as a subcortical dementia.
- Therapies for Parkinson's disease are aimed at ameliorating the loss of dopamine.
- Huntington's disease, a genetically inherited condition, is characterized by motor symptoms, including sudden jerky movements. It leads to a constellation of cognitive disturbances in executive functioning, spatial processing, and memory, as well as emotional symptoms that include depression, irritability, impulsivity, and aggression. This behavioral profile, along with damage in the basal ganglia, leads these difficulties to be classified as a subcortical dementia.
- Mixed-variety dementias have symptoms that are a blend of those seen in cortical and subcortical dementias.

- The most common kind of mixed-variety dementia, vascular dementia, results from the cumulative effect of many small strokes. The condition has a variable profile of neuropsychological dysfunction depending on the severity of the strokes and the brain regions affected.

Multiple Sclerosis

- Multiple sclerosis (MS) is the most common demyelinating disease. It seems to be caused by a genetic vulnerability combined with exposure to an environmental pathogen, which is as yet undefined.
- Because the regions of brain tissue affected differ among individuals, some variability in the cognitive dysfunction is observed, although sensory and motor deficits, along with difficulties in memory, conceptual reasoning, and attention, are common.

Epilepsy

- Epilepsy, which is caused by synchronous and atypical firing of nerve cells, usually results from exposure to toxins, head injury, or metabolic disturbances.
- Cognitive deficits are usually seen in tasks dependent on the region from which the seizures originate. Sometimes changes in personality occur as well.
- Typically, epilepsy is treated by drugs that dampen down the activity of the nervous system; in more severe cases, surgery is employed when the focus of the seizure can be clearly defined.

Disorders of Conscious Awareness

- Severe brain injuries may result in unresponsive wakefulness syndrome, in which the patient is awake but shows no behavioral responsiveness and thus is

seemingly unaware. Such conditions present difficult challenges for doctors and families.

- Brain imaging may yield important clues to the level of cognitive processing possible by persons in states of unresponsive wakefulness.

Chapter 17

Cognitive Neuroscience and Society



[Public Perceptions of Neuroscience](#)

[Neuroscience and Education](#)

[Neuroscience and Social Inequality](#)

[Neuroscience and the Law](#)

[In Focus: Can Brain Imaging Detect Lies?](#)

[Neuroscience and Performance Optimization](#)

[Neuroscience and the Marketplace](#)

[The Neuroscience of Morality](#)

[Summary](#)

Can a person be sentenced to life in prison for crimes committed while a juvenile? Prior to 2010, when the US Supreme Court considered this issue in the groundbreaking case of *Graham v. Florida*, the answer in the United States was yes. Although uncommon in practice, at the time the court heard the *Graham* case, there were 129 prisoners in the United States serving life sentences without parole based on crimes committed while the perpetrators were less than 18 years of age (Liptak, [2010](#)). That practice ended with the Supreme Court's decision in *Graham*, a decision that relied, in part, on evidence from neuroscience studies of the adolescent brain.

The case involved a Florida teenager, Terrance Graham, who at the age of 16 attempted to rob a restaurant along with three other teenagers. Graham was charged as an adult, as Florida law allows for 16- and 17-year-olds at the prosecutor's discretion, and he pled guilty. He was sentenced to three years' probation, the first year of which was served in county jail. About six months after his release, when Graham was nearly 18, he was allegedly involved in another burglary, again with two accomplices and this time involving a home invasion. Police found guns in Graham's possession, a violation of the terms of his probation. Based partly on the fact that Graham was now a repeat offender who had violated probation, the Florida trial court judge sentenced Graham to the maximum penalty, life in prison without the possibility of parole.

The issue before the Supreme Court was whether the eighth amendment to the US Constitution, which prohibits "cruel and unusual punishment," should be interpreted to disallow imprisoning someone for life, without any hope of release, for actions they committed while a juvenile. The court had already ruled on juvenile justice issues in 2005 in *Roper v. Simmons*, determining that the eighth amendment prohibits applying the death penalty to offenders whose crimes were committed while they were less than 18 years old.

Both the American Medical Association (AMA) and the American Psychological Association (APA) filed briefs in the Graham case. Citing dozens of studies, the AMA argued that the adolescent brain is structurally and functionally immature, particularly in regions associated with impulsivity and behavioral control (AMA, [2009](#)). The APA's argument was based primarily on psychological evidence that, compared to adults, adolescents exhibit less mature behavior, are more susceptible to external influences such as peers, and also have greater capacity for reform (APA, 2009). Like the AMA, the APA also cited studies from cognitive neuroscience pointing toward the immaturity of the adolescent brain.

The Supreme Court's 6-3 decision ultimately determined that it is unconstitutional under the eighth amendment to imprison someone for life with no parole for nonhomicide crimes committed as a juvenile. While the majority opinion included many nuances in reasoning, in part it appeared to accept and deem relevant the evidence presented by the AMA and APA. Penning the court's majority opinion, Justice Anthony Kennedy wrote, "developments in psychology and brain science continue to show fundamental differences between juvenile and adult minds," acknowledging that "parts of the brain involved in behavior control continue to mature through late adolescence" (Graham v. Florida, p. 17). Based in part on this reasoning, the majority concluded that the reduced culpability of juveniles made life imprisonment without parole a disproportionately severe punishment for a nonhomicide crime. In a 2012 case, Miller v. Alabama, the Supreme Court determined that even for homicides committed while a juvenile, life imprisonment without parole is unconstitutional.

While generally viewed as victories for juvenile advocates, the court decisions in the Roper, Graham, and Miller cases raise complex questions about the potential role of neuroscience evidence in the justice system and beyond (Buchen, [2012](#)). For example, if the adolescent brain is immature, can the government on that basis require adolescents to seek parental permission for reproductive health decisions, such as abortions? Scientists have argued that such health decisions depend on different contextual factors and therefore different decision-making mechanisms than impulsive criminal behavior (Steinberg et al., [2009](#)). More generally, how conclusive must scientific evidence be in order for courts to rely upon that evidence in making decisions with long-lasting consequences for individuals and society at large?

The brain as an object of study seems to capture the public imagination like no other topic in science. Aided by striking color images intended to show "the brain in action,"

media stories stoke the public's interest in research that promises to reveal the secrets of human thought and behavior. Everyday people may look to neuroscience for a deeper understanding of their own behaviors or the behaviors of those around them. Scholars are actively exploring the potential relevance of cognitive neuroscience research to critical domains of society including education, business, and the law, as seen in this chapter's opening vignette. Meanwhile, profiteers may seek to capitalize on the public's eagerness for "all things neuro" in order to make a dime. Yet, public enthusiasm notwithstanding, the science of the brain is very much in flux, as material from all the prior chapters can attest.

A central challenge, then, is to navigate the public dissemination of knowledge about neuroscience research such that legitimate findings with important societal implications can be separated from hype, even as knowledge in the field shifts from year to year. For neuroscientists, this can mean stepping back from specific, narrowly tailored projects to regain a sense of the broader societal and ethical implications of their research. Scientists can also help by exercising humility, for example by avoiding the suggestion that neuroscience will soon deliver definitive answers to thorny questions about human nature that have plagued thinkers for millennia. Laypeople, for their part, should approach information about neuroscience with a critical eye, neither breathlessly accepting all the promises of neuroscience nor cynically discarding all of them. Achieving a balanced critical understanding is not easy for either the scientist or the layperson, particularly as the field is still rapidly developing. But such balance will be essential as the societal implications of neuroscience research come under closer scrutiny.

Public Perceptions of Neuroscience

Public discourse about neuroscience largely takes place through mainstream media, such as newspapers, magazines, TV, blogs, and other internet sites (see Beck, [2010](#); O'Connell et al., [2011](#); Racine et al., [2010](#)). Translating scientific findings through such

media is challenging, largely because research methods can be highly technical and findings complex, while at the same time the public feels a strong stake in conclusions with implications about human nature (Illes, 2010). Analyses of media reports about neuroscience generally indicate a low level of accuracy, though accuracy depends on the quality of the news outlet and the topic being covered (van Atteveldt et al., [2014](#)). Meanwhile, neuroscientists report ambivalent attitudes toward press coverage of their research, appreciating the potential benefits to themselves and the public while harboring apprehension about inaccurate representation of their work (Allgaier et al., [2013](#)).

What does the general public want to know about neuroscience, and how much do they believe about what they read or hear? One study surveyed readers of a neuroscience blog to determine which topics they were most and least likely to read about (Herculano-Houzel, [2002](#)). Topping the list were topics about basic cognitive functions such as memory, learning, and emotion, as well as cross-cutting themes like consciousness and development. Readers reported being least interested in reading about sex differences in the brain, and were only modestly interested in reading about diseases of the brain (see [Figure 17.1](#)).

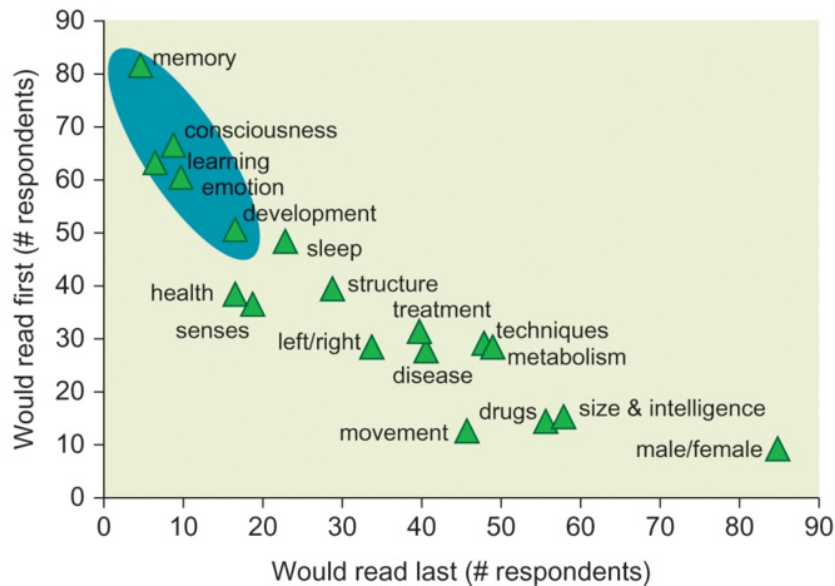


Figure 17.1 Interest in neuroscience among laypeople.

Readers of a neuroscience blog indicated which topics they would most and least like to read about from a list of 18 topics.

(from Herculano-Houzel, [2003](#))

Media reports about emerging neuroscience technology tend to present enthusiastic views that convey few details about the technology (Racine et al., [2006](#), [2010](#)). Yet, readers also appear to have a somewhat nuanced view of the role of technology. For example, nonexperts responding to an online survey agreed that neuroimaging could be used to diagnose medical conditions such as tumors, but not “to find out what you are thinking” or “to find out your political opinion” (see [Figure 17.2](#); Wardlaw et al., [2011](#)). Respondents also indicated that they would be willing to have their own brains scanned for scientific research or for medical diagnosis, but not as part of a job interview or for advertising research (see [Figure 17.3](#)). Nevertheless, significant proportions of the public still endorse “brain myths,” such as the belief that we only use a small part of our brains or that listening to Mozart will increase intelligence (Herculano-Houzel, [2002](#); Pasquinelli, [2012](#)).

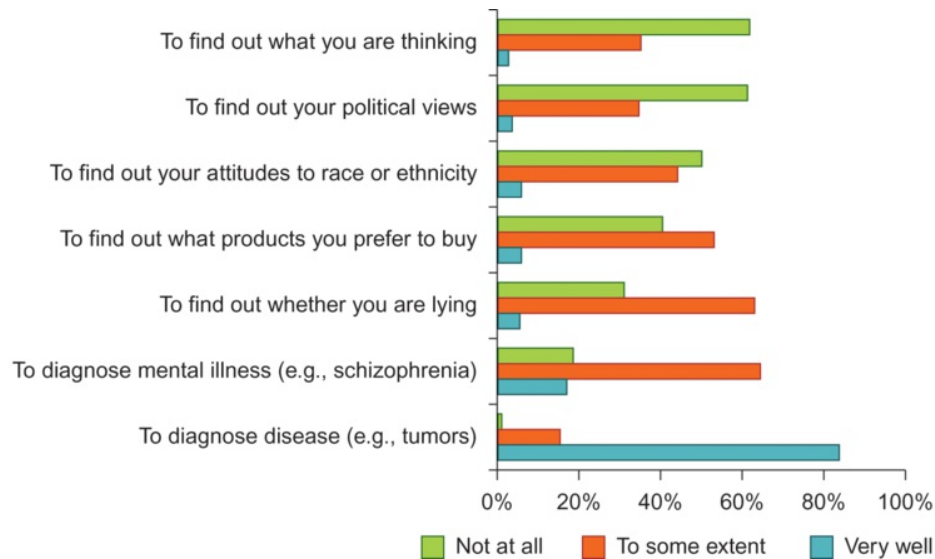


Figure 17.2 What can brain imaging tell us?

Members of the public indicated their opinions about how well neuroimaging technology can achieve different aims.

(from Wardlaw et al., [2011](#))

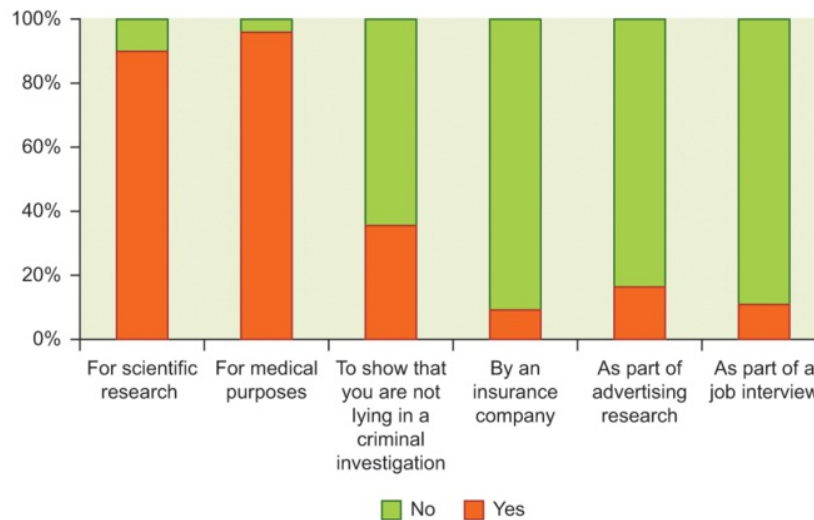


Figure 17.3 When would you allow your brain to be scanned?

Members of the public indicated whether they would be comfortable having their brains scanned for different purposes.

(from Wardlaw et al., [2011](#))

Some research implies that when people are evaluating an explanation of human behavior, they may be unduly influenced by irrelevant references to neuroscience

information. In a seminal study (Weisberg et al., [2008](#)), researchers gave undergraduates the task of judging explanations of human cognition and behavior. Some of the students received explanations that incorporated verbal references to brain regions, even though the brain references did not actually add any explanatory information. Even undergraduate students who had completed a cognitive neuroscience course judged poor-quality explanations as better when a brain region was mentioned compared to when it wasn't. However, graduate students and postdoctoral researchers in neuroscience were not tricked when irrelevant neuroscience information was added. They judged the bad explanations to be just as bad (and good explanations to be worse, possibly because these experts noticed how irrelevant the neuroscience information was to even the good explanation!). The researchers argue that brain-related information has a "seductive allure" that makes flimsy arguments seem more substantial, particularly to audiences who are less adept at evaluating them.

This "seductive allure" study led to follow-up studies intended to better understand the ways in which people are persuaded by neuroscience information (e.g., Fernandez-Duque et al., [2015](#); Weisberg et al., [2015](#)). Some researchers pointed out that it's not clear whether the "seductive allure" is due to the specific neuroscience content of the explanations or people's more general faith in explanations that sound more like hard science (Farah and Hook, [2013](#); Weisberg et al., [2008](#)). For example, one study found that people with PhDs in nonscience fields were more impressed by an abstract in sociology or anthropology that contained an irrelevant scientific equation compared to the same abstract without the equation (Eriksson, [2012](#)). Yet, a subsequent study found that the allure of neuroscience in explaining behavior seems to be even greater than the allure of hard science more generally. In the study, nonexperts increased their ratings of an explanation of behavior even more when it referred to brain information than when it referred to information from other sciences such as math or genetics (Fernandez-Duque et al., [2015](#)).

Neuroscience findings are often reported alongside vivid colorful images of the brain, reflecting advances in neuroimaging technology in recent decades. To what extent do images themselves sway an audience to believe the findings? One seminal study found that participants rated conclusions from either a fictional cognitive neuroscience study or a real media report as more believable when the verbal description was accompanied by a brain image (McCabe and Castel, [2008](#)). A related study found that the perceived three-dimensionality of a brain image, that is, its concreteness or solidity, contributes to its persuasiveness (Keehner et al., [2011](#)). However, subsequent research has found that images may not be as influential as these earlier studies suggested (Gruber and Dickerson, [2012](#); Hook and Farah, [2013a](#); Michael et al., [2013](#); Schweitzer et al., [2013](#)). For example, studies of mock jurors found an influence of neuroscience information on decision making regardless of whether the information was presented in a verbal or pictorial form (e.g., Schweitzer et al., [2011](#); Greene and Cahill, [2012](#)). Given the conflicting evidence, presently it seems that brain images may have undue impact on reasoning only in limited circumstances (Baker et al., [2017](#)).

Given the public's general faith in brain science, it is not surprising that participants in cognitive neuroscience research studies can seem gullible about what may be deduced about their thoughts during a study. For example, researchers at an elite North American university asked their undergraduate participants to sit in a mock scanner made out of old parts, which they referred to as "SpinTronics" technology (see [Figure 17.4](#); Ali et al., [2014](#)). The researchers then used an old magicians' trick to make it seem that their technology was able to determine which numbers participants had secretly written down on a piece of paper. Whereas before the "scanning" experience, participants were skeptical about the ability of SpinTronics to decode their thoughts, afterward they reported higher levels of belief in the technology and low levels of skepticism – even the half of the participants who were currently taking a class that emphasized critical thinking about cognitive neuroscience! The researchers argue that

the vividness of a personal experience with neuroscience technology can lead participants to suspend critical reasoning.



Figure 17.4 Experiences with brain imaging technology are persuasive.

Researchers placed participants in a mock scanner that they dubbed “SpinTronics” and which was made from old parts such as a hair salon hood. Participants were surprisingly willing to believe that the scanner could “read their thoughts”.

(from Ali et al., [2014](#))

An additional factor determining the persuasiveness of a neuroscience finding is whether the finding reinforces or counters a person’s preexisting beliefs. In one study, researchers presented participants with fictional brain imaging findings seeming to indicate that human fetuses either did or did not have brain activity associated with the perception of pain (Scurich and Shniderman, [2014](#)). Participants were more likely to be persuaded by whichever finding supported their preexisting views about abortion. That is, pro-choice participants were more persuaded by the fictional evidence that showed no fetal brain response to pain, while anti-abortion participants were more persuaded by the fictional evidence that showed that there was a fetal brain response to pain. Thus, despite the potential for neuroscience to transform the way people think about

controversial societal issues, people may instead selectively rely upon neuroscientific information to support what they already believe (O'Connor and Joffe, [2013](#)). This pattern of results likely reflects the well-known [confirmation bias](#), in which people tend to remember and seek out information consistent with their prior beliefs, while ignoring or downplaying information that is at odds with what they already think (Nickerson, [1998](#)).

Neuroscience and Education

A partnership between education and cognitive neuroscience is logically appealing: after all, education is centrally concerned with developing cognitive functions such as learning, memory, and reasoning, while cognitive neuroscience provides a framework for understanding the mechanisms that sustain those functions (Carew and Magsamen, [2010](#); Goswami, [2008](#); Sigman et al., [2014](#)). Furthermore, the educational system provides a venue for children of all ages to learn about the brain and behavior.

Generally, evidence suggests that teachers are enthusiastic to learn about neuroscience for its own sake as well as for possible impact on classroom techniques. While teachers may be susceptible to some of the “brain myths” that are prevalent among the general public, such as the belief in “right brain versus left brain learning” (Dekker et al., [2012](#); Howard-Jones, [2014](#); Lindell and Kidd, [2011](#)), they tend to believe that neuroscience is relevant to their goals as educators (Hook and Farah, [2013b](#); Pickering and Howard-Jones, [2007](#)). Given their natural intellectual curiosity and professional motivation, primary and secondary school teachers are an especially appropriate audience for neuroscientists aiming to increase public awareness about the brain (Dubinsky, [2010](#)).

Children, too, are naturally interested in neuroscience (see [Figure 17.5](#); Cameron and Chudler, [2003](#); Sperduti et al., [2012](#)). One successful interchange between neuroscience and education has focused on efforts to introduce neuroscience material and activities to children in the classroom. Exposure to a “brain awareness”

presentation by a visiting neuroscientist, emphasizing the plasticity of the brain and its relevance to learning and memory, led children in fourth through sixth grade to report more positive attitudes toward science and a heightened belief in the idea that their own intelligence can change (“I can get smarter if I try”; Fitzakerley et al., [2013](#)).



Figure 17.5 Children are eager to learn about the brain and how it can make them think and feel.

Source: RubberBall Productions/Getty Images.

Neuroscience may have the potential to inform educational theory and practice in specific targeted areas, such as reading and math instruction or the understanding of learning disabilities. Consideration of each of these areas in depth is beyond the scope of this chapter, but here we use the study of reading to illustrate how findings from neuroscience are relevant to educational practice.

As discussed in [Chapter 8](#), children require formal instruction in reading, in contrast to spoken language, which children develop spontaneously when raised in a typical social environment. Early reading is a very laborious process, and a significant percentage of children struggle with reading well beyond the early years. Approximately 10% of children are affected by dyslexia (Norton et al., [2015](#); Peterson

and Pennington, [2012](#)). Because literacy is so critical in modern societies, there is strong motivation to understand why some children have more trouble learning to read, and to identify them early so that beneficial interventions might be applied. Early intervention is especially important because the gap between good readers and poor readers tends to widen over childhood, as good readers get much more reading practice than those who struggle (Mol and Bus, [2011](#)).

Certain neural abnormalities are known to accompany dyslexia in children and adults. For example, as reviewed in [Chapter 15](#), dyslexia is associated with reduced activity in left-hemisphere frontal, parietal, and temporal lobe regions relevant to language processing (Christodoulou et al., [2014](#); Kovelman, 2014; for review, see Norton et al., [2015](#)). Yet, there are different ways to interpret these brain-behavior correlations: the neural differences between poor and good readers could be the cause of individual differences in reading skill, or they could be the consequence of different amounts of reading experience, as good readers are known to read more (Krafnick et al., [2014](#)). Educational implications could differ depending on which of these two scenarios is true.

One way to get around the “cause-or-consequence” question is to examine children who have not yet started to read, but who possess certain risk factors for dyslexia, including a family history or poor performance on tests of pre-reading skills, such as awareness of the phonemes of language. Some neural differences associated with dyslexia risk have been found even in pre-reading kindergarteners, suggesting that the neural differences precede the reading difficulties rather than following from them (Raschle et al., [2012](#); Saygin et al., [2013](#)). Even more crucially, several studies have found that neural measures can predict future reading skill better than behavioral measures alone ([Figure 17.6](#); Bach et al., [2013](#); Maurer et al., [2009](#); see also Hoeft et al., [2007](#), [2011](#); Molfese et al., [2007](#); Myers et al., [2014](#)). These latter findings in particular suggest that cognitive neuroscience measures could ultimately help to pinpoint children in need of early intervention before they start down a path of struggling in school.

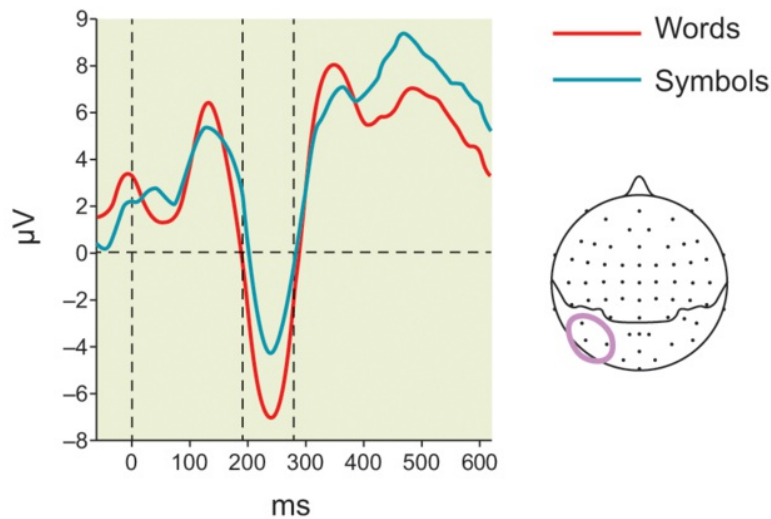


Figure 17.6 Using neural measures to predict reading performance.

Kindergarteners showed stronger N1 neural responses to visually presented words (red line) compared to symbols (blue line). The degree of this effect predicted individual differences in reading performance in second grade, over and above behavioral measures of phonological awareness in kindergarten.

(from Bach et al., [2013](#))

Findings such as these reflect the potential for neuroscience measures to add to our understanding of individual differences in cognition that directly impact school performance. There are practical limitations to consider, such as whether underfunded school systems could afford the equipment and expertise necessary to administer neuroscience-based screening for reading-related risk. Likewise, ethical questions arise, such as whether there are negative consequences of a child being labeled as at risk for reading problems before even entering the school system, or whether it is appropriate to “medicalize” individual differences in learning that may exist along a continuum (e.g., Cuthbert, [2015](#); Elliott and Gibbs, [2008](#)).

As with the joining of any two specialized fields, one challenge in “neuro-education” is the differing domains of expertise of neuroscientists and educators. While it is often appreciated that scientists have specialized knowledge of research techniques and findings, educators themselves have specialized knowledge of classroom

challenges, teaching techniques, and the role of education within broader society. Likewise, the two may have different goals: the scientist may be concerned with understanding basic mechanisms, while the educator may be concerned with what works in a classroom of diverse learners.

Furthermore, some critics have questioned whether cognitive neuroscience can really add any information relevant to education that isn't already provided by traditional cognitive psychology (e.g., Bruer, [1997](#), [2008](#); Cuthbert, [2015](#)). For example, if cognitive psychology research tells us that multisensory experience (visual, auditory, tactile, vestibular) is beneficial for learning, does it really add anything to know which brain regions carry out those processes? Or does the inclusion of neuroscience information simply add a hard-science gloss, a "seductive allure," that makes the psychology findings seem more impressive?

The answer to this question hinges on one's goals. If the goal is simply to see whether an educational intervention leads to better academic achievement, it may not matter which brain systems underlie that achievement. As an analogy, most of us don't really care how a computer works as long as it does the things we want it to. On the other hand, say the goal is to determine whether a particular educational intervention aids learning through rote memorization or more generalized higher-order thinking skills. In this case, determining which brain regions become more involved over the course of learning could yield relevant information. If learning occurs through rote memorization, we would anticipate increased activation with learning in brain regions that support the specific perceptual, sensory-motor, or multimodal processes underlying the skill. However, if learning involves more abstract or relational skills, then with learning, we would anticipate increased activation in frontal brain regions, and potentially the hippocampus. Although hypothetical, this example illustrates how brain imaging evidence could yield deeper insights into how and why a particular educational intervention may be effective.

Neuroscience and Social Inequality

One sobering area of research focuses on the effects of poverty on brain development and cognition (for reviews, see Hackman et al., [2010](#); Lipina and Posern, [2012](#); Noble, [2014](#); Raizada and Kishiyama, [2010](#)). This research has relevance not only to education, but also to society at large, highlighting the social inequalities that stack the deck, biologically and cognitively, against children coming from impoverished backgrounds. The research also raises questions about which interventions may be effective in reducing those discrepancies (see [Figure 17.7](#)).

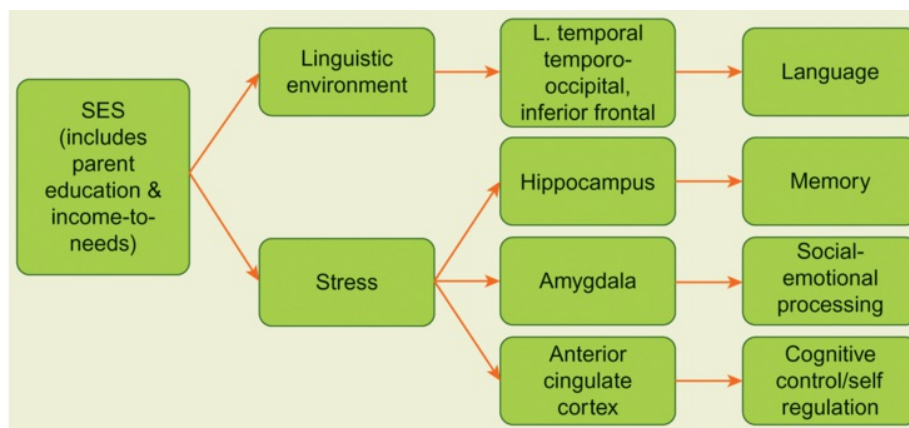


Figure 17.7 Possible paths linking socioeconomic status (SES) to altered cognitive outcomes.

Lower SES may affect language environments in the home, in turn affecting the development of temporal and frontal lobe regions that support language development. In addition, stress associated with lower SES can affect the hippocampus, amygdala, and prefrontal cortex, thereby impacting cognitive functions carried out by those regions. Interventions can potentially target many different levels, such as poverty itself, language input or stressors in the low SES environment, or cognitive functions themselves.

(from Hackman et al., [2010](#))

Although it has been known for some time that children from poorer backgrounds have generally lower odds of educational success (e.g., Bradley and Corwyn, [2002](#);

Sirin, [2005](#)), recent studies have more closely examined the particular domains of cognition that best differentiate those from lower- versus higher-income brackets. These studies have generally compared children with lower versus higher socioeconomic status (SES), often defined on the basis of family income and parental education and occupation. For example, in a study of kindergarten children in Philadelphia public schools, lower SES was associated with poorer performance on tasks of executive function and language, whereas memory, spatial cognition, and visual cognition were not significantly associated with SES (Noble et al., 2005; see also Noble et al., [2007](#)).

Given the degree to which poorer cognitive functioning is associated with lower income status, it should not be surprising to learn that neural measures also show differences between children with different socioeconomic backgrounds. Studies of brain anatomy using structural MRI have reported SES-related reductions in cortical thickness in the left inferior frontal gyrus and right anterior cingulate cortex, regions involved in executive control (Lawson et al., [2013](#)). Others have found that children from lower SES backgrounds are characterized by smaller gray-matter volumes in hippocampus and cortical regions of the temporal lobe, areas associated with memory and emotional processing (Jednoróg et al., [2012](#)). Studies also show SES-related differences in ERP measures of attention, such as reduced amplitude of early components that measure attention, the P1 and N1 components, in low SES children (see [Figure 17.8](#); Kishiyama et al., [2009](#); Stevens et al., [2009](#)), and in fMRI measures of frontal lobe activation during tasks of executive function and emotion regulation (Liberzon et al., [2015](#); Sheridan et al., [2012](#)). In a study that assessed both anatomical differences and standardized test performance in lower and higher SES groups, lags in the anatomical development of frontal and temporal regions accounted for about one-fifth of the group differences in test performance, indicating that delayed brain development may contribute to SES-related achievement gaps (Hair et al., [2015](#)).



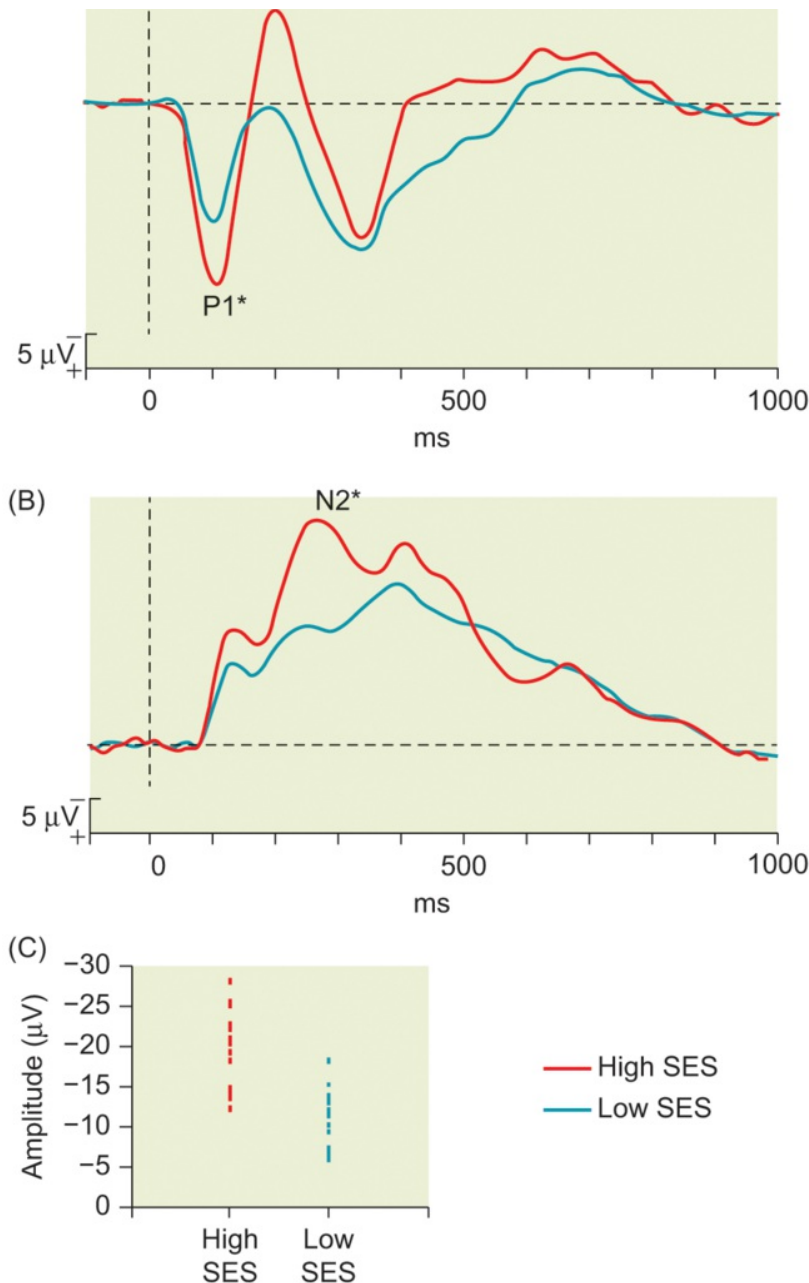


Figure 17.8 Socioeconomic status affects early visual responses to images.

ERP responses to visual images in a series of standard (repeated) and novel pictures, shown separately for high and low SES children. (A) shows the reduced P1/N1 in response to standard pictures among low SES children, whereas (B) shows the reduced N2 response to novel pictures. (C) illustrates data for the novelty N2 effect for each individual participant, illustrating the variability and overlap between groups.

(from Kishiyama et al., [2009](#))

Crucially, studies have found that such differences in brain anatomy and development are disproportionately pronounced at the lowest end of the SES continuum (Hair et al., [2015](#); Noble, Houston et al., [2015](#)). In other words, while SES may predict brain anatomy and behavioral performance at all levels of the continuum ranging from very low to very high SES, the largest effects are evident at the very low-income end. Put another way, a stepwise increase in SES has a bigger beneficial effect on brain structure and performance at the lowest end of the scale. This implies that special attention be paid to targeting interventions toward those families living significantly below the poverty line (Hair et al., [2015](#)).

Such findings should not be used to perpetuate negative stereotypes about people from poorer backgrounds. First, there is a large range in outcomes within any income bracket; at any given level of income, some children do much better and others much worse (see [Figure 17.8](#)). Furthermore, even if one focuses on the group averages that reflect poorer performance and reduced cortical thickness for children from low SES backgrounds, the fact that differences exist does not mean that they are carved in stone. Quite the opposite: indeed, many researchers aim to understand the mechanisms that lead to poorer outcomes for poorer children so that effective interventions can be designed.

Two potential mechanisms have been proposed to account for SES-related differences in cognition and brain function: language stimulation in the home, and stress. These explanations are not mutually exclusive. The language-based explanation proposes that children in low SES homes generally receive lower quantity and quality of language input (e.g., Hart and Risley, [1995](#); Hoff, [2003](#), [2013](#); Huttenlocher et al., [2010](#)). Differences in language input could account for why children as young as 18 months already have poorer language development if they come from low-income families (Fernald et al., [2013](#); see also Noble, Engelhardt et al., [2015](#)). Exposure to more complex language could improve a child's vocabulary and also have further-reaching effects on developing working memory, because more complex sentences place a greater demand on working memory. In support of the language-input explanation, one

study found that complexity of language use in the home (measured by coding a videotaped dinner conversation) increased with SES and also predicted children's prefrontal cortex activity during an executive functioning task (Sheridan et al., [2012](#)). The language-based explanation is often referred to as a “deficit” explanation because it conceptualizes the problems in terms of deficits within the environments of children from poorer backgrounds.

Another explanation, the stress explanation, focuses on the high levels of chronic stress experienced by many people living in poverty. Rather than being a “deficit” explanation, the stress explanation is more focused on understanding the presence of factors that contribute to adversity. Evidence for this account of the SES–cognition relationship comes from several sources. First, experimental studies with nonhuman animals have demonstrated the pernicious effects of chronic stress on brain development, particularly in the frontal lobe regions that are relevant to both executive functions and language in humans (e.g., Arnsten, [2009](#), Arnsten et al., [2015](#)). Animal studies have also clearly demonstrated detrimental effects of stress on medial temporal lobe regions such as hippocampus and amygdala, critical for memory and emotion reactivity, respectively (McEwen and Gianaros, [2010](#)). In addition, studies of children from lower-income homes found that higher levels of the stress hormone cortisol predicted poorer levels of cognitive performance (Blair et al., [2011](#); see also Sheridan et al., [2012](#)), lending support to the idea that chronic stress and cognitive performance are closely linked.

A recent study found that even the short-term stress of an upcoming exam had negative consequences for performance on a task of attentional control and altered functional connectivity between prefrontal cortex and other brain regions (Liston et al., [2009](#)). Such research suggests that the best way to face your exams may be to “stay chill” (while, of course, still studying hard). Interestingly, the effects were eliminated one month after the stressor had passed, indicating reversibility of at least some of the effects of stress on frontal lobe functions. Of course, the acute stress of an exam may not

be directly comparable to the chronic and multifaceted stresses that affect people from low-income backgrounds. Nevertheless, the study supports the idea that some effects of stress on prefrontal function may be reversed when the stressor is removed.

The linguistic and stress-based explanations are not mutually exclusive. For example, it may be that both home-language input and environmental stress are important causal factors, working either separately or jointly to influence brain development. Furthermore, evidence supporting either of these explanations doesn't necessarily rule out additional factors that may link lower SES to poorer outcomes, such as the potential role of sensitive parental care, nutrition, sleep, environmental toxins, or more broadly chaotic homes and neighborhoods (e.g., Hackman et al., [2010](#)). As with many correlational studies, it can be difficult to tease apart multiple factors that might contribute to a given phenomenon, in this case SES-related differences in brain development and behavioral performance.

Research on interventions is the next logical piece of the puzzle in understanding the causal pathways that connect poverty and cognitive and neural outcomes. A wide range of interventions has shown some promise in enhancing executive functions in young children, including computerized training programs, yoga, and martial arts (Diamond and Lee, [2011](#)). Training in aspects of self-regulation – including the ability to focus attention, set goals, think through problems, and control emotional reactions– appears to be beneficial, as shown in a study that randomly assigned kindergarten classes to a self-regulation program or a control condition (Blair and Raver, [2014](#)). Kindergartners in some classrooms received the training program, a curriculum called “Tools of the Mind” that was designed to develop self-regulation through a focus on reflective thinking (e.g., thinking through both correct and incorrect solutions to problems), individualized goal-setting together with the teacher, cooperative problem solving with peers, and dramatic play tied to literature, which is intended to develop social-emotional skills. Children in “Tools of the Mind” classrooms showed greater improvements in executive functions as well as reduced levels of cortisol, compared to

the control classroom children, who completed their normal school curriculum (Blair and Raver, [2014](#)). Moreover, the improvements in the “Tools of the Mind” classrooms were more pronounced for lower-income schools.

Other interventions target the whole family, rather than focusing solely on the child or the school setting, reasoning that home environments can be critical in supporting cognitive development. Such interventions are sometimes referred to as “two-generation” interventions because they target both the child and the parents. For example, one study randomly assigned lower-income families whose preschool children were enrolled in a Head Start program to either a training program or a control condition (Neville et al., [2013](#)). Families in the training program received both attentional-skills training for the children as well as training for the parents in managing household stress and engaging in responsive parenting. There were two control groups, one that received primarily the child-focused attention training (with minimal parent training) and another that received no intervention other than the typical Head Start program. After only eight weeks of training, children in the family-based intervention showed significant improvements in ERP-based measures of attention compared to both of the control groups (Neville et al., [2013](#)). These results, and others, indicate ways in which interventions targeting both parents and children can facilitate neural and cognitive development in low-income children (Neville et al., [2015](#)).

Many would argue that a robust societal response to poverty must go well beyond invoking cognitive neuroscience, for example addressing the roles that social systems play in perpetuating inequality. As such, interventions may be appropriately targeted not only at the level of brain and cognition, but also at larger-scale social systems. Nevertheless, if interventions inspired by cognitive neuroscience can ultimately enhance children’s academic achievement, especially that of children from lower SES backgrounds, they may aid in breaking a cycle of persistent inequality across generations.

Neuroscience and the Law

Inherent tensions exist between the legal system and neuroscience because the manner in which decisions are made within each is quite different. In science, we speak of probabilities, rejecting the null hypothesis (and accepting the premise that the manipulation in our experiment had an effect) if the pattern of results occurs less than five times out of 100 by chance. But juries must make definitive decisions on guilt and innocence; they cannot make probabilistic pronouncements such as “We the jury conclude that the chances are 80 out of 100 that the defendant is guilty.” Furthermore, in the legal system, the jury hears only select evidence, that is, the evidence that either the prosecutors or the defense attorneys wish to present (and that the judge deems legally admissible). Other information that might be relevant is excluded from consideration. In contrast, scientific reviewers of a research report will insist that the authors cite all the relevant studies on a given topic. Moreover, scientists can test theories of how the brain and mind work by designing new experiments, which creates more evidence. Juries, needless to say, can only consider evidence that already exists.

This disconnection between neuroscience and the law can sometimes put them at odds. As one example, consider the case of Rodney King, an African-American man who was beaten by four Los Angeles police officers in 1991 while being arrested after a high-speed chase. That King was severely beaten was not in doubt; a negligence claim King brought against the city stated that the beating had resulted in 11 skull fractures and permanent brain damage. Criminal charges were brought against the four officers for willfully and intentionally using unreasonable force. During the trial, King was a witness for the prosecution and recounted his memory of the beating. However, as a cognitive neuroscientist, you should find the idea of him giving testimony a bit odd. How likely is it that King would accurately remember the details of such a severe beating? As we learned in [Chapter 9](#), memories need to be consolidated, and typically any closed head injury, such as the one sustained by King, would disrupt that consolidation process. This would likely preclude him from remembering not only the

beating, but also some of the events just prior to it. How then could King have managed to testify? Days after the event, a videotape of the incident made by a bystander was played numerous times on local news station. King likely saw the video at some point after the actual events transpired, and may have based his testimony in part on the video. So, shouldn't the defense attorneys for the police officers have brought in a cognitive neuroscientist as an expert witness to question the veracity of King's memory? But if they had done so, the defense would have had to concede that King's memory was faulty because the officers had beaten him so severely, evidence that the defense would likely not want to underscore for the jury.

Despite such disconnects between scientific and legal approaches to evidence, in more recent years, cognitive neuroscience has started to impact the way in which evidence is considered within the judicial system. As seen in the narrative that opened this chapter, one critical area in which law and neuroscience have intersected is in juvenile justice, specifically the question of whether adolescents have reduced culpability compared to adults (see Steinberg, [2009](#), for review).

Culpability, in legal terms, refers to the degree to which a person is held responsible for an action. To understand gradations of culpability, consider the range of charges brought against someone for the killing of another person. For example, if a driver consumes alcohol above the legal limit and then strikes and kills a pedestrian, he or she may be charged with involuntary manslaughter. The charge is "involuntary" because there was no intent to kill the pedestrian, but nonetheless a reasonable person should have known that alcohol impairs driving ability, and that driving with such a high blood alcohol level is illegal. In contrast, first-degree murder implies a greater degree of culpability. Such charges are brought when a person deliberately planned to kill another, for example when a person murders another to benefit from the deceased's insurance policy. Penalties are higher for first-degree murder compared to involuntary manslaughter due to the different level of culpability. Typical jail terms in the US for involuntary manslaughter range from fines to up to eight years imprisonment, while

terms for first-degree murder range from decades to life imprisonment, and in severe cases even the death penalty. As this discussion illustrates, the ability to understand the consequences of one's actions (e.g., drinking and driving) and the ability to plan are two crucial capabilities within a legal framework.

A large body of recent work has considered whether adolescents should be considered less legally culpable, that is, whether they have "diminished capacity" by virtue of their immaturity. We assume in many other contexts that adolescents are not yet mature. For example, in the United States, we do not allow them to vote, drink, or drive until reaching a certain age. The question then becomes whether their diminished capacity should be considered in a criminal context. In certain cases in the United States, when an adolescent commits a crime, prosecutors will petition to have the person transferred to an adult court to be tried as an adult, as in the example involving Terrance Graham in the chapter's opening vignette. Prosecutors often argue that most adolescents know right from wrong. The consequences of trying an adolescent defendant in the adult system can be life-changing, because sentences in the juvenile system tend to be less punitive and there are more opportunities for rehabilitation compared to the adult system. In fact, in some countries, even juveniles who commit first-degree murder are provided with lesser sentences. For example, in a case in New Zealand in which two teenage girls killed one of their mothers (events depicted in the movie 1994 *Heavenly Creatures*, which helped to bring Kate Winslet to fame), the girls were sentenced and released after about five and a half years.

Similarly, within a legal framework, people are deemed less culpable if they commit a crime under duress. For example, a person is typically considered less culpable if he commits a robbery when someone else held a gun to his head than if he committed the robbery of his own volition. One issue that has been raised is whether "duress" for teenagers might be different than "duress" for adults. In particular, peer pressure exerts a very strong influence during the teenage years in a way that is distinct from such pressure as an adult (Steinberg and Monahan, 2007). From that perspective,

is trying to impress one's friends by engaging in a rash and daring act, like taking a car for a joyride, an action that occurs under "duress" that is specific to this developmental period in life?

Cognitive neuroscience is starting to aid in our understanding of these and related legal issues. As we learned in [Chapter 15](#), the development of the brain is more protracted than we had assumed a decade ago, with gray-matter thinning and white-matter expansion continuing into the middle 20s. These data alone suggest that the brain is not yet fully developed in youth, which likely provides opportunity for future growth and rehabilitation. Such a concept is important under the law, as sentencing often involves consideration of whether someone has been affirmed through testimony to be basically a good and upstanding citizen, as compared to a repeat offender with antisocial or violent tendencies. If the brains of adolescents are not yet fully formed, then any tendency toward being a "good" or "bad" person may likely not yet be formed.

However, is there any evidence that these developmental processes are related to concepts relevant in a legal setting: understanding the consequences of one's actions, and the ability to tune out distracting information especially of a social nature? In fact, they seem to be. For example, in a study performed in the laboratory of one of the authors of this text, the more 16–17 year olds activated dorsolateral prefrontal cortex during performance of an executive function task, the greater was their self-reported control over their behavior in real life (Andrews-Hanna et al., [2011](#)). While correlation is not causation, this result suggests that ongoing brain development may be required for certain mental skills relevant to the law. Moreover, such a relationship was not observed for young adults, suggesting that other factors, besides the ability to engage this region of prefrontal cortex, influence self-control behaviors after adolescence (Andrews-Hanna et al., [2011](#)). Similarly, youth who report they are more able to resist peer pressure also show greater activation in dorsolateral prefrontal cortex and associated frontal lobe control regions when watching videos of movements associated with anger (Grosbras et al., [2007](#)).

Aspects of maturing brain anatomy have also been linked to cognitive control in children and adolescents. For example, increased structural integrity of white-matter tracts within the prefrontal cortex predicted 7- to 13-year-old children's ability to inhibit an inappropriate response (Madsen et al., [2010](#)). Additionally, youth show greater activation in reward-related regions when they play a "risky" driving video game with a friend watching than when they play alone, a pattern not observed in adults (Chein et al., [2011](#)). This finding speaks to the importance of social influences on decision making during adolescence and how such decision making engages brain systems distinct from those in adults.

Because of this new and growing science on adolescent brain development, cognitive neuroscientists, including the first author of this text, have served to provide expert testimony in court regarding crime by youth. Cognitive neuroscientists can bring evidence of protracted brain development to the courts and others in the juvenile system, providing insights into the limitations of adolescent decision making compared to adults. This evidence does not suggest that youth cannot tell "right" from "wrong," but rather suggests that they have diminished capacity to control actions compared to adults, which should be considered in how they are treated within the justice system.

A more controversial intersection of cognitive neuroscience and the law concerns defense arguments along the lines of "his bad brain made him do it." In some cases, witnesses for the defense will introduce evidence regarding brain scans suggesting particular immature or damaged regions of the brain. This use of neuroscience evidence in individual cases, with the intent to diminish a specific defendant's perceived culpability, is distinct from the use of neuroscience evidence to influence general approaches to whole classes of people, such as adolescents. At present, there is no way to categorically diagnose if a particular person has a "bad" brain. Consider, for example, what makes a bad car. Poor braking distance? Poor pick-up? A large turning radius? Poor visibility from the driver's seat? Similarly, we cannot yet say what a "defective" or "bad" brain would be. Which variables would be relevant? Too little

white matter? Not enough pruning of gray matter? Lack of connectivity between regions? Furthermore, because there is normal and continuous variation in neural measures within any group of healthy people, it's not realistic to think that a dividing line can be placed neatly between "normal" and "abnormal."

Cognitive neuroscience also interfaces with the law in some other major realms: detecting truth or lies (see In Focus box feature), understanding altered decision making in people with mental health disorders (Meynen, [2013](#)), and predicting recidivism. The work in this last area is particularly fascinating and raises complex ethical issues. For example, one study of adult male sex offenders found that increased brain activation in the anterior cingulate cortex while performing a Go/No-Go task, often used to measure inhibitory control, was related to a decreased recidivism over a four-year period. Moreover, ACC activity during the inhibitory control task could better predict recidivism than other factors such as age and level of psychopathy (Aharoni et al., [2013](#)). If such evidence were to accumulate with additional future studies, what would be the implications for the criminal justice system? For example, could neuroscience evidence be used for making parole decisions about individual prisoners? Are there ethical dimensions to using a biological risk factor to predict a prisoner's likelihood of reoffending? As this discussion attests, and as noted by a US Presidential Bioethics Commission on this topic (Jones et al., [2014](#)), the integration of cognitive neuroscience evidence into the legal system still faces many challenges.

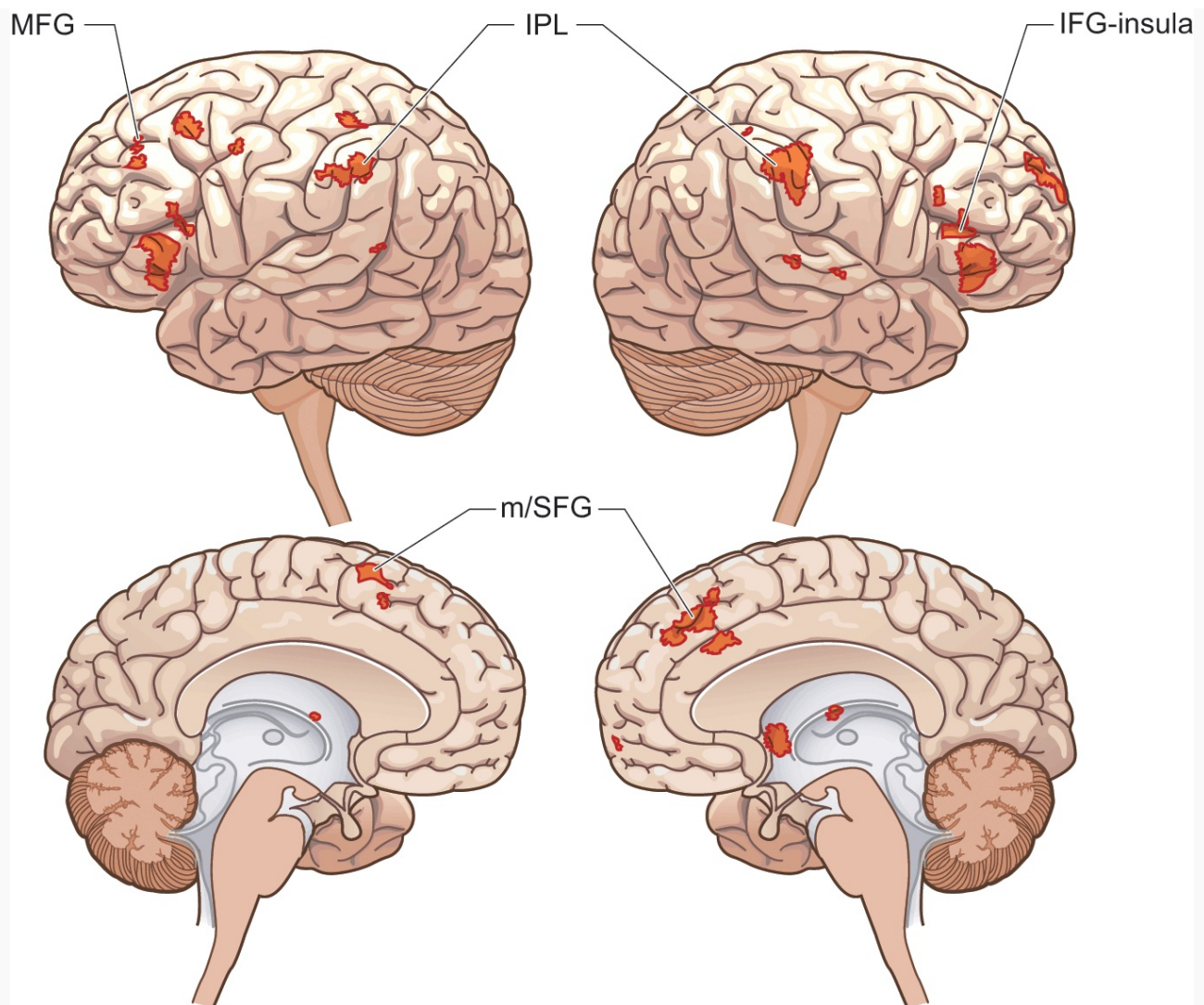
In Focus: Can Brain Imaging Detect Lies?

Can you read my mind? More specifically, can you tell when I am lying? Humans have evolved the capacity to intentionally deceive one another, a cognitively sophisticated act that requires simultaneously representing in the mind both the truth and a counterfactual state of affairs (the lie) and then attempting to get another person to believe what one knows to be untrue. Along with the ability to deceive comes the need to detect deception in order to avoid being duped. Yet,

humans are surprisingly poor judges of when others are lying (e.g., Bond and DePaulo, [2006](#)). Can brain imaging help to distinguish truth from lies? While it may not be helpful in everyday life – you are unlikely to use fMRI to discern whether your partner really did have to work late that night – there is active debate about whether fMRI could be useful in detecting lies in other applied contexts, such as determining the credibility of witnesses in court cases, job candidates in employment decisions, or suspects in military interrogations (for reviews, see Abe, [2011](#); Farah et al., [2014](#); Langleben and Moriarty, [2013](#); Rusconi and Mitchener-Nissen, [2013](#)).

In earlier work using EEG methods, researchers took advantage of a paradigm called the [guilty knowledge test](#) (GKT; Farwell and Donchin, [1991](#)). The GKT is applicable in situations in which certain information would be known only by a person involved in a crime. For example, imagine that an assault was committed with an iron pipe. Experimenters could present a participant with stimuli representing a variety of weapons, including a gun, a knife, a rope, and the iron pipe. Theoretically, a person with knowledge of the crime would have a different physiological response (such as elevated P300 amplitude) to the iron pipe than the other weapons, due to the memory trace involving that weapon, whereas innocent people would have similar responses to all of the weapons. Although there is some evidence that EEG responses can identify such concealed information (e.g., Farwell et al., [2014](#)), this method has drawbacks that limit its applicability. For example, it only works in situations in which there is private knowledge limited to a criminal suspect and the investigators. In many crimes, information about the crime is either publicly known, in which case even innocent people could show the “guilty” knowledge, or relevant details are unknown even to the investigators, in which case they wouldn’t know how to include those details in a GKT (for additional critiques, see Rosenfeld, [2005](#)).

Basic research on the neuroscience of deception has investigated whether patterns of localized brain activity can distinguish between truth-telling and lying in various experimental settings. For example, in some studies using a variation on the GKT, participants are asked to choose one of two playing cards. These cards are then presented in a series along with other cards that the participant had not seen. For each card in the series, the participant was asked, “Do you have this card?” and was instructed to deny having either card (e.g., Langleben et al., [2002](#)). A comparison of brain activity between the chosen (and falsely denied) card and the nonchosen (and truthfully denied) card could, in theory, distinguish between truth-telling and lying. In another type of experiment, intended to better reflect a crime scenario, participants were asked to “steal” either a watch or a ring, and then scans were taken while they answered questions about the hypothetically stolen and nonstolen objects (Kozel et al., [2005](#)). While results differ somewhat across studies using these kinds of methods, a meta-analysis found a set of regions consistently more activated for lying than truth-telling (see [Box Figure 17.1](#); Farah et al., [2014](#)). Interestingly, several of these areas, such as dorsolateral and ventrolateral prefrontal cortex, are known to be involved in the exertion of effortful control, which is plausibly more engaged when participants lie.



Box Figure 17.1 Brain activity associated with lying.

A meta-analysis found a distributed set of regions in frontal and parietal cortex that respond more strongly when a participant is telling an instructed lie compared to the truth in a lab experiment. These regions included middle frontal gyrus (MFG), inferior frontal gyrus (IFG), medial superior frontal gyrus (mSFG), and inferior parietal lobe (IPL).

(from Farah et al., [2014](#))

Critics have raised several concerns about the potential application of this line of research to applied contexts, such as the courtroom (Farah et al., [2014](#); Rusconi and Mitchener-Nissen, [2013](#); Tennison and Moreno, [2012](#)). Some concerns involve the generalizability of the findings outside of the lab setting.

First, the paradigms used in the research are fairly different from those that are likely to occur in, for example, real-world criminal contexts. Participants in the experiments are instructed to lie, so by lying they are actually complying with the rules and expectations of the experimenters. It is not clear how this kind of instructed lying compares with self-motivated, antisocial lying. Relatedly, lying about which playing card one viewed has quite a different emotional weight than lying about a murder, for example. There is very little at stake in most lab studies of lying. In addition, participants in lab studies of the neural basis of deception have generally been typical college students who have not extensively rehearsed the specific lies (though for an exception, see Jiang et al., [2013](#)). Results could be quite different for criminals or habitual liars, who may have practiced their lies over long periods of time and thus may be able to produce them with less effort.

Another critical issue in the applicability of fMRI-based lie detection is the question of its accuracy, particularly when considered on an individual basis. It is one thing to determine that lies, on average across a sample of participants, differ statistically from truth-telling in their associated patterns of brain activity. It is another thing to examine data from an individual person and to determine categorically whether that individual is lying or not.

Ideally, it would be desirable to have a method that detects lies 100% of the time when they occur (i.e., has high sensitivity to lies) at the same time as indicating lies 0% of the time when the person is telling the truth (i.e., has high specificity for lies, or, in other words, a low false-positive rate). It is difficult to pin down precise estimates for sensitivity and specificity based on existing studies, but some studies suggest a high false-positive rate, as high as 67%, for fMRI-based lie detection (Kozel et al., [2009](#)). Needless to say, a high false-positive rate is troubling when potentially serious real-world consequences, such as a criminal conviction or loss of employment, are at stake. In any case, the evaluation of whether fMRI-based lie detection has useful applications will

hinge on achieving more precise estimates of its sensitivity and specificity (Langleben and Moriarty, [2013](#)).

At the time of this writing, no US court has admitted fMRI-based evidence of lying into evidence in any court case, although a few courts have been asked to do so and have declined (Farah et al., [2014](#); Langleben and Moriarty, [2013](#)). This pattern fits with US courts' reluctance to admit evidence from the polygraph test, which is an older method of attempting to detect lying using peripheral psychophysiological measures of autonomic arousal, such as skin conductance, heart rate, or blood pressure. Given the current state of knowledge, there is not a consensus among scientific experts that either fMRI-based lie detection or the older polygraph testing are valid in distinguishing truth from lies.

Currently, in a legal context, judgments about the credibility of witnesses are left almost entirely in the hands of the jury (or the judge in trials without jury). At least in the United States, courts appear disinclined to undermine the role of the jury members in making these credibility determinations (Langleben and Moriarty, [2013](#)). Yet, jury members are not perfect arbiters of credibility, being subject to all of the imperfections of humans judging one another's words, actions, and demeanor (Schauer, [2010](#)). Thus, despite significant scientific and ethical concerns about the use of fMRI-based lie detection at the present time, the acknowledgment of serious flaws in the current system of jury-based credibility determination leaves the door open for possible technological solutions in the future.

Neuroscience and Performance Optimization

If you have ever ridden on an airplane, you have probably hoped that your pilot was functioning at optimal levels of cognitive performance. While planes have "autopilot" functions that control some aspects of the flight under routine conditions, planes are ultimately under the control of human beings who, one would hope, are alert, receptive

to relevant incoming sensory information, able to draw upon stored knowledge and skills, mentally flexible, and prepared to make quick and accurate decisions under changing conditions. Most of us are not pilots, but many of us have driven cars, an activity whose safe implementation also requires many of these same abilities. From a more sobering perspective, national security and defense departments have a strong interest in understanding how soldiers' minds can function optimally under tremendously stressful and dangerous conditions (e.g., Huang and Kosal, [2008](#); Royal Society, [2012](#); Tennison and Moreno, [2012](#); Tracey and Flower, [2014](#)). What can cognitive neuroscience research findings contribute to enhancing performance in such occupations, and what ethical issues arise?

It has been known for decades that pharmacological manipulations can affect cognition. For example, you probably do not need this book to tell you that alcohol impairs thinking, and presumably you would rather not fly with a drunk pilot. But what about drugs that can enhance rather than impair cognition? If you have ever imbibed caffeine to keep yourself alert for an important exam or presentation, you are already familiar with the concept of pharmacological optimization of cognition. Recent evidence suggests that stimulant drugs, such as methylphenidate and modafinil, can have beneficial effects on some aspects of attention, learning, and memory. The effects tend to be small and vary significantly across people, and the mechanisms are not well understood (Husain and Mehta, [2011](#); Morein-Zamir and Sahakian, [2011](#); Smith and Farah, [2011](#)). Yet, such drugs have been used in applied contexts, such as to combat fatigue in long military missions (Tennison and Moreno, [2012](#); Tracey and Flower, [2014](#)).

While pharmacological enhancement of cognition has probably existed since people first began to ingest herbs, new technology now also allows the brain to be manipulated through direct magnetic or electrical stimulation. Specifically, stimulation methods such as TMS and tDCS are being explored for their potentially beneficial effects on cognitive performance, raising questions about the applicability of these technologies in high-performance occupations (Hamilton et al., [2011](#)). TMS has been used as a

therapeutic tool for specific conditions such as depression, and is under investigation for application to Parkinson's disease and schizophrenia (Pascual-Leone et al., [2011](#)). Recent studies suggest that cognitive performance can also be improved in healthy people through such stimulation methods. For example, in one study, researchers applied tDCS to the left dorsolateral prefrontal cortex in normal volunteers, and found improved performance (compared to sham and right dorsolateral stimulation) on the Remote Associates Test, a standard test thought to tap verbal association ability and general intelligence (Cerruti and Schlaug, [2009](#)). Other studies have found that brain stimulation through tDCS can improve vigilance, perception, and motor skill learning (see Coffman et al., [2014](#), for review).

Beyond directly manipulating the brain, additional applied research has aimed to use neural measures to identify a person's mental state, such that intervention could be applied when the person falls into a nonoptimal state that could lead to dangerous errors. For example, if technology could identify a pilot's level of alertness, a warning signal could be triggered when the pilot's brain shows signs of drowsiness. To be useful, such technology would need to operate in "real time," such that relevant neural measures could be instantaneously extracted rather than computed off-line at a later time. Recent developments in computational and statistical methods have made such "real-time" monitoring of the brain possible. EEG measures are particularly well suited for this task, because they are sensitive to the brain's overall level of arousal and could be more realistically implemented in applied settings such as a cockpit compared to other neural measures such as fMRI (Tracey and Flower, [2014](#)). Researchers are also using EEG measures to determine a pilot's mental workload, that is, the extent to which limited-capacity processes are being taxed by the various tasks at hand, such as monitoring the changing weather, the incoming reports from air traffic control, the presence of other aircraft, and the plane's mechanical systems (e.g., Borghini et al., [2014](#)).

Although fMRI is less practical in many applied settings – due to its cost and susceptibility to interference from ferrous metals in the surroundings – researchers are also investigating how real-time fMRI can be used as a source of biofeedback to help participants better control brain functioning (Caria et al., [2012](#); deCharms, [2008](#)). For example, in one study using real-time fMRI, participants learned to control activity in the rostral anterior cingulate (rACC) at will (responding to explicit instructions to increase or decrease activity in this region), and researchers found that these volitional changes in rACC activity were correlated with alterations in sensitivity to a thermal pain stimulus (deCharms et al., [2005](#)). Additional research found that, using the feedback from real-time fMRI, participants could learn to modulate activity in visual cortex in a manner that increased visual sensitivity (Scharnowski et al., [2012](#)).

Human capacities of perception and motor control have also been extended by so-called [brain-machine interfaces \(BMIs\)](#), referring to direct communication between the brain and artificial devices. For example, recall that [Chapter 4](#) discusses the use of BMIs in remote “mind control” of robotic devices by paralyzed people. By decoding action commands from the patient’s motor cortex via implanted electrodes, technology can allow those commands to move a cursor on a computer screen or even a robotic arm (for reviews, see Nicolelis and Lebedev, [2009](#); Thakor, [2013](#); Wander and Rao, [2014](#)).

Due to improvements in communication technology, such mental control over robotic devices can extend over long distances. For example, in one experiment, a monkey’s brain in North Carolina was able to control a robotic device in Japan (aided by implanted electrodes, as well as the experimenters’ computation and engineering, of course; Lebedev et al., [2011](#)). Researchers are now working to see whether noninvasive measures of brain function, such as real-time fMRI, can control remote devices. Indeed, in one demonstration, ongoing fMRI measurements of a person in Israel imagining motor actions were used to control a robot in France (see [Figure 17.9](#); Cohen et al., [2014](#)). Defense agencies, such as the US Defense Advanced Research Projects Agency

(DARPA) are now interested in how such BMI technology could further military objectives (Miranda et al., [2015](#)).

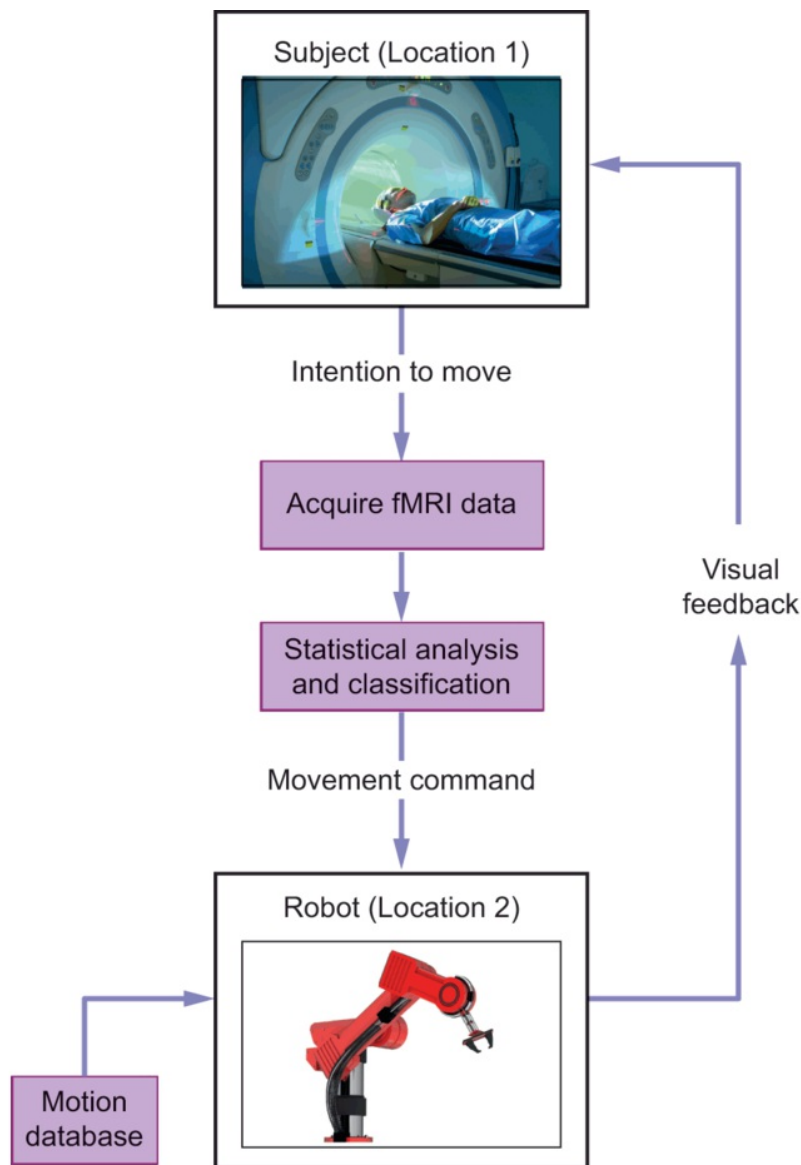


Figure 17.9 Steps involved in remote control of robotic devices using fMRI.

From Cohen et al., [2014](#). Photo inserts from Getty Images.

While scientists and engineers make progress on technical fronts, ethical examination is also in order. Few would argue with the desirability of enhancing the capacity of paralyzed people to act upon the world, and likewise few would argue with the aim of enhancing the mental performance of commercial airline pilots. After all, the goal of a civilian pilot is to transport people and cargo as safely and efficiently as

possible. Yet, when the technology extends to military applications, the intentions are less benign and therefore the ethical issues become more complex. For example, is it a benefit to society if BMIs could allow military commanders to control robotic devices on remote battlefields, or if a soldier's neural activity could be manipulated toward national security ends? Bioethicists refer to technology's [dual use dilemma](#), namely the possibility that any technology can potentially be used for both beneficial and malevolent purposes (Royal Society, [2012](#)).

Moreover, additional ethical issues involving coercion arise in both civilian and military contexts. When it becomes possible to enhance cognition through artificial means (e.g., pharmaceutical or stimulation techniques), does it become expected and thereby implicitly coerced? Could it be permissible for airlines to require pilots to take cognition-enhancing drugs, or for long-haul trucking companies to require truck drivers to be monitored by EEG or stimulated by tDCS? In the military context, the possibility of explicit coercion is even greater, as soldiers face enormous pressure for conformity and respect for the chain of command (Royal Society, [2012](#); Tennison and Moreno, [2012](#)).

Furthermore, evidence suggests that drugs that supposedly enhance cognition are becoming more widely used outside of medical contexts or contexts that arguably involve public safety, such as driving, aviation, or the military. Specifically, there is growing concern about college students' use of stimulants to enhance test performance (Chatterjee, [2007](#); Racine and Forlini, [2010](#); Ragan et al., [2013](#)). [Cosmetic neurology](#), the use of neural intervention to improve cognition in healthy people, is a term intentionally akin to cosmetic surgery, the use of surgery to beautify healthy people (Chatterjee, [2007](#)). While some aspects of the debate are scientific – such as disagreements in the literature about whether such interventions really do improve performance and what their side effects might be – other considerations extend beyond the facts and involve issues of values and ethics. In addition to the concern about implicit coercion mentioned previously, another ethical concern relates to the ability of

more affluent people to “buy a better brain,” exacerbating social inequalities that are already known to impact neural and cognitive development to the disadvantage of lower-income people (Hamilton et al., [2011](#); Metzinger and Hildt, [2011](#)).

Neuroscience and the Marketplace

All over the world, people are engaged in buying and selling. Whether it is selling greens at a local bazaar, hot dogs at a ballgame, electronic equipment over the internet, or construction contracts to major industries, people frequently exchange money for goods and services. Clearly the human brain has the capacity to represent abstraction of value, such as the value represented in money, and to evaluate and act upon the perceived value of various products or services. Marketing, which aims to get products into the hands of buyers, has long been influenced by research in social psychology on the art of persuasion and by research in cognitive psychology on judgment and decision making. Can cognitive neuroscience add anything useful to shed light on how a consumer makes a decision to buy?

[Neuro-marketing](#) is a term typically used to describe the use of neuroscience information for purposes of marketing (for reviews, see Ariely and Berns, [2010](#); Javor et al., [2013](#); Plassmann et al., [2012](#); Reimann et al., [2011](#)). In theory, basic neuroscience research could potentially further our understanding of the cognitive, emotional, and social factors that influence a decision to buy. Meanwhile, as scientific findings in this area are still developing, numerous “neuro-marketing” companies have popped up promising to apply neuroscientific knowledge to help companies better understand and reach their desired consumers. Why rely on a focus group or opinion survey to tell you what the customers think, when you could use a brain scan that might reveal the customers’ true feelings to a greater degree?

Of course, there are a number of reasons why brain scans may not be just what marketers need to better understand their consumers. First, neuroimaging is very expensive compared with survey or focus group studies. The extra knowledge gleaned,

above and beyond what could be gleaned from self-report surveys, would have to be pretty valuable, as measured ultimately by more product sales, to justify the cost of neuroimaging to a company's marketing budget. Furthermore, while neuroimaging has the potential to reveal aspects of people's cognition that they don't have conscious access to, or don't wish to admit on a survey, the connection between a neuroimaging finding and a conclusion about the person's mental state is not so straightforward. For example, if you want to know how much consumers like your product, maybe it is better to simply ask them, or observe how much they buy, rather than to measure activity in the amygdala or nucleus accumbens and then attempt to draw a conclusion based on assumptions about how that brain activity reflects the mental state of liking.

While the direct and immediate application of neuroscience findings to the practice of marketing may be premature, numerous intriguing studies have examined brain activity related to product value and choice. For example, one line of research has examined ways that the brain is affected by tricks used in marketing and sales. In one study, participants tasted different wines while lying in a scanner and rated how much they liked each one (Plassmann et al., [2008](#)). Along with each sip of wine, the participants were also told how much the wine cost. The same wines were reported as tasting better when they were paired with a higher price. Moreover, activity in the medial orbitofrontal cortex (OFC), which is thought to represent valuation (see [Chapter 12](#)), was also affected by the wine's fictitious price, although activity in primary taste regions was not (see [Figure 17.10](#)). These latter findings suggest that it was not the taste itself that was altered by the wine's price, but the hedonic value attributed to that taste by the OFC.

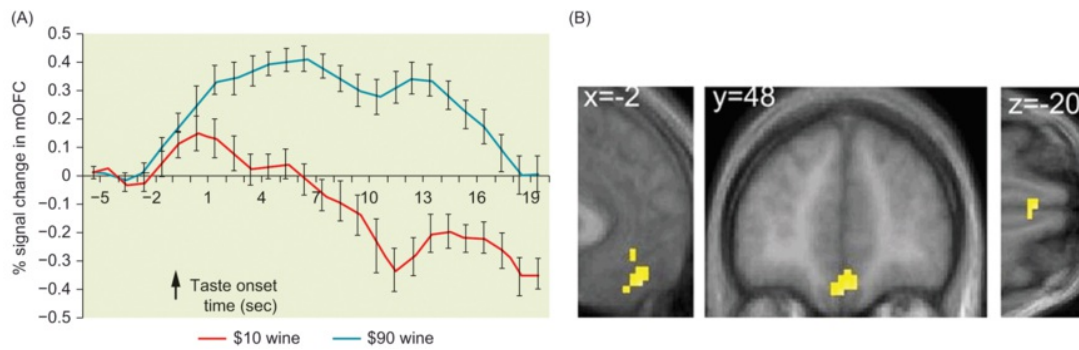


Figure 17.10 The brain responds to pricing.

The medial OFC responds more strongly to the same wine's taste when it is paired with a \$90 price tag compared to a \$10 price tag.

(from Plassmann et al., [2008](#))

Other research indicates that the medial OFC codes the value of a stimulus in a way that relates to “willingness to pay,” an important index for marketers (Plassmann et al., [2007](#)). Hungry participants viewed pictures of 50 different tasty snacks and, on experimental trials, were allowed to bid on how much they would pay for those snacks. In control trials, participants viewed the same pictures but were forced to bid a particular amount rather than making their own choice of bid. In this way, the experimenters aimed to isolate the brain activity associated not just with the food pictures and their associations, but with the mental calculation of deciding how much one would be willing to pay for each item. Results indicated that activity in the medial OFC increased along with the participant's bid in the free-choice condition, and showed lesser activity in the forced-bid condition in which the participant did not get to decide how much to pay. These results converge with other findings indicating that the OFC codes the value of a stimulus, and this study implies that it does so in ways that could predict consumer behavior (e.g., Hare et al., [2009](#); Kable and Glimcher, [2007](#); Rolls et al., [2008](#)).

Both of these studies illustrate how scientists can investigate people's decisions about products and purchases, but they also demonstrate the limitations in direct applications for businesses interested in increasing sales. For example, from a

business's point of view, it may be enough to know that participants' ratings of the wine are influenced by its price, and it may not add anything of practical consequence to know that the OFC indexes this effect. Likewise, companies may be more interested in knowing what factors influence willingness to pay, rather than caring that the OFC tracks that willingness. Thus, once again we see that the scientific desire to understand mechanisms – how the brain represents information and makes decisions – differs from the goals of another constituency in society, in this case business, which tends to be concerned primarily with a practical consequence such as the bottom line.

While most of our discussion of neuro-marketing has centered around whether brain measurements can assist marketers in understanding the minds of their consumers, another way of thinking about neuro-marketing is to consider the ways in which the term “brain” is used as a marketing or sales ploy to convince people to hand over some of their hard-earned money. A prime example is the proliferation of “brain fitness” programs, specifically targeted toward the elderly, many of whom are concerned about cognitive decline (Chancellor and Chatterjee, [2011](#); Papp et al., [2009](#)). Numerous software packages can be purchased for hundreds of dollars that promise to “train the brain” to stave off dementia. In the most general sense, the brain surely can be trained, as is evident in normal learning and in studies of cognitive enrichment in older populations (e.g., Schmiedek et al., [2010](#)). However, in many cases, the claims of companies that sell brain-training programs are not supported by any evidence of the effectiveness of that specific program. In other cases, claims are backed only by evidence produced by those with a financial stake in the company that makes the product (Chancellor and Chatterjee, [2011](#)). Where “brain branding” is concerned, let the buyer beware, indeed.

The Neuroscience of Morality

Many of the most vexing questions for society are moral questions. What does it mean for a society to be fair and just? How should we conceptualize right and wrong? How

should we judge the morality of other people's actions, and how should we make moral choices ourselves? Questions of morality and ethics have long been central concerns of philosophy and religion, and it seems at first to be almost absurd to imagine that scientific knowledge could tell us something about the right way to behave. Yet, in recent years, a number of neuroscientists and evolutionary biologists have attempted to grapple with thorny questions involving morality and the brain.

Studies of morality from a neuroscience standpoint have approached the issue in a variety of ways, focusing on various aspects of the broad and complex concept of morality (Decety and Wheatley, [2015](#)). Some have considered how the concept of fairness, or equal distribution of resources, evolved in our primate ancestors. Some have focused on understanding the origins of pro-social behavior, that is, behavior oriented toward others rather than the self, such as parenting or cooperative behavior. Related is the concept of altruism, acts of apparent self-sacrifice to benefit others. Other researchers have studied the neural basis of empathy and its potential connection to moral behavior. Still others have examined how regions of the brain crucial for decision making are activated in the face of challenging moral dilemmas.

From a broad evolutionary perspective, the development of morality is closely tied to group living. For animals such as primates that live in social groups, behavior is regulated in part by norms about what constitutes appropriate behavior. For example, a monkey who hoards food for himself risks becoming ostracized from his group and losing out on the benefits of cooperation, whereas one who shares may stand to reap benefits of future resource sharing by others (although he may be a bit hungry after sharing with others). Due to our evolutionary history that was shaped by the pressures of group living, it is likely that we share some rudimentary foundations of moral behavior with our fellow primates (for reviews of the evolution of moral behavior, see Delton and Krasnow, [2015](#); Prétôt and Brosnan, [2015](#)).

Although the concept of "justice" can seem highly abstract, empirical studies show that monkeys are able to evaluate fairness at some level. In a much-cited study, New World capuchin monkeys refused to participate in exchanges with experimenters if they

saw other monkeys getting a bigger reward for doing so (Brosnan and de Waal, [2003](#); see also van Wolkenten et al., [2007](#)). Specifically, the monkeys refused to exchange tokens in order to get a cucumber when they saw another monkey getting a much more desirable grape in exchange for the same token; however, the monkeys would settle for a cucumber if the other monkey was only getting a cucumber too (see [Figure 17.11](#)). Researchers argue that this inequity aversion, or displeasure at unfairness, reflects at least a rudimentary moral sense in monkeys (for reviews and critiques, see Bräuer and Hanus, [2012](#); Brosnan, [2013](#)). It will come as no surprise to anyone with a brother or sister to learn that young children, too, possess a basic sense of fairness quite early in life (e.g., Geraci and Surian, [2011](#); Sloane et al., [2012](#)).



Figure 17.11 A sense of fairness is evident in other primate species.

A capuchin monkey rejects a cucumber after seeing another monkey get a more desirable grape reward for the same action.

(from Brosnan and de Waal, [2014](#))

While it is one thing to bristle at the injustices done to oneself, it is quite another to be troubled by injustices done to others. To be offended when others are treated unfairly

requires a sense of justice that transcends immediate self-interest. Many researchers are skeptical about how consistently other primate species exhibit evidence of this capacity (Bräuer and Hanus, [2012](#); Brosnan and de Waal, [2014](#)). (Indeed, one might argue that humans achieve this level of morality only in their better moments.) Here the concept of empathy becomes relevant. Might the neural mechanisms that support empathy, as reviewed in [Chapter 13](#), provide a way that we can feel one another's injustices in the same way that we feel their physical pain?

Empathy, as you recall from [Chapter 13](#), can involve a number of different components, including the ability to feel what another person (or animal) feels (sometimes referred to as emotional contagion), the motivation to help another in distress, and the cognitive ability to take the perspective of another (Decety and Cowell, [2014](#), [2015](#)). On the surface, the relationship between empathy and morality may seem straightforward: perhaps we can become morally outraged on another's behalf when we feel and understand their pain. Yet, neural mechanisms of empathy do not always act according to principles of fairness. For example, neural responses to the pain of others are enhanced when those others are related to us, familiar to us, or members of our social in-group, compared to when those others are strangers or out-group members (e.g., Cheng et al., [2010](#); Langford et al., [2010](#); Molenberghs et al., [2016](#)). Thus, while mechanisms of empathy may indeed foster certain pro-social behaviors, such as looking out for our friends and relatives, empathetic responses can also be biased in ways that favor those closest to or most similar to us (Decety and Cowell, [2014](#), [2015](#)). For these reasons, empathy alone may not serve as the basis for a truly fair (unbiased) sense of justice.

Some research supports the idea that cognitive perspective-taking (mentally taking the point of view of another person) may be a better route than emotional empathy to achieve fair and equitable treatment of others. For example, one study assessed individual differences in justice sensitivity, which is intended to index how likely a participant is to act in the face of injustice, in participants whose brains were scanned

while they viewed pictures of morally bad scenes (e.g., pulling someone's hair) and morally good scenes (e.g., helping someone off the floor; Yoder and Decety, [2014b](#)). People who scored high on justice sensitivity assigned more blame to actors in the morally bad scenarios and more praise to actors in the morally good scenarios, compared to people who scored low on justice sensitivity. Additionally, individual differences in justice sensitivity predicted activity in the temporoparietal junction, a region known to be linked with understanding the mental states of others (see [Chapter 13](#)). However, justice sensitivity did not predict activity in regions linked to emotional salience or action observation. These results, along with others (e.g., Yoder and Decety, [2014a](#)), are consistent with the idea that concern with justice may be more closely tied to cognitive aspects of perspective-taking than to emotionally empathetic reactions to morally good or bad actions.

The role of emotion in moral decision making has long been a topic of study (e.g., Haidt, [2001](#)). Undoubtedly, when we are faced with a scenario that we judge to be morally wrong, such as news of a massacre of innocents, our moral judgment contains strong emotional components, such as anger, sadness, disgust, and fear. It is no surprise, then, that emotion-related regions of the brain, such as the amygdala and insula, are activated under these scenarios (e.g., Shenhav and Greene, [2014](#)). Moreover, situations of moral disgust cause facial expressions similar to those produced when tasting something unpleasant (see [Figure 17.12](#); Chapman et al., [2009](#)). But what about situations in which we are faced with challenging moral dilemmas in which right and wrong are more ambiguous? Do we engage in purely “cold” cognitive reasoning to reach a conclusion, or does emotion enter our moral decision-making process?

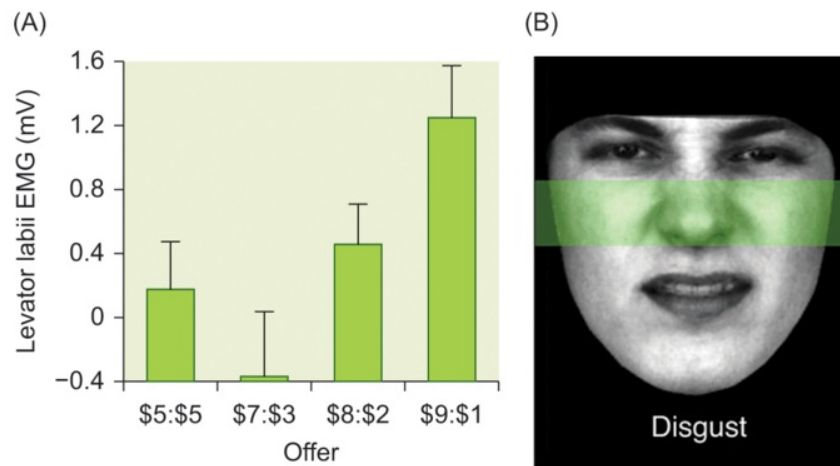


Figure 17.12 Unfair financial offers elicit facial expressions of disgust.

Activation of the levator labii (nose-wrinkling) muscle is greater for unfair offers in an economic game, such as offering to divide \$10 between two people according to a \$9/\$1 split.

(from Chapman et al., [2009](#))

Questions about the role of varied brain regions in moral reasoning have been addressed using hypothetical moral dilemmas (for review, see Christensen and Gomila, [2012](#)). In the most famous of these dilemmas, known as the trolley dilemma, the participant must decide whether it is morally permissible to push a large man off a bridge in front of an oncoming trolley in order to stop that trolley from killing several other people who are standing on the tracks (see [Figure 17.13](#)). Generally, people find it difficult to endorse (hypothetically) pushing the man off the bridge, even though costing his one life would save the lives of others. This dilemma is perceived as more difficult than a structurally similar dilemma in which flicking a switch would divert the trolley to another track, killing one person, rather than continuing on its current path, where it would kill several. Although both cases involve the same trade-off in lives, there is something more personal about giving the man a shove off the bridge, compared to flicking a switch, and that personal element heightens the moral dilemma.



Figure 17.13 An example of a scenario used in research on moral reasoning.

In the famous trolley dilemma, the participant must decide whether to sacrifice one life in order to save five lives. In one scenario (shown on the left), the decision is enacted by flicking a switch to divert the trolley, and in another scenario (shown on the right), the decision is enacted by pushing a man off a bridge to block the trolley.

In one of the first fMRI studies to examine the role of brain regions in resolving such moral dilemmas, researchers found a set of regions, including medial frontal gyrus and posterior cingulate gyrus, that was more activated in response to the difficult personal-moral dilemmas (such as pushing a man off the bridge to save others), compared to impersonal-moral dilemmas (flicking a switch; Greene et al., [2001](#); see also Greene et al., [2004](#)). At the time, the researchers interpreted these results as pointing to the role of emotion in the personal moral dilemmas (Greene et al., [2001](#)). However, later interpretations focused more on conceptualizing these areas as part of the default mode network, which is involved in internally directed thinking (Greene, [2015](#)). Regardless of the precise interpretation, it does appear that different subsets of brain regions are involved in resolving moral dilemmas depending on the extent to which personal elements are incorporated.

More recent research has focused in more depth on the role of medial OFC (sometimes referred to as vmPFC) in integrating different kinds of information, including both emotional cues and more strictly cognitive “costs-and-benefits”

reasoning, often referred to as utilitarian reasoning. For example, one fMRI study asked participants to read scenarios describing certain actions and to evaluate either their emotional responses or their utilitarian responses (Hutcherson et al., [2015](#)). To rate emotional responses, participants used a scale from “very appalling” to “very appealing.” To rate utilitarian responses, participants used a scale from “very costly” to “very beneficial” and were instructed to consider costs and benefits to the individuals depicted as well as society at large. In a later segment of the study, participants read more complex scenarios that were constituted from the various actions that they had previously rated, and were asked to indicate the appropriateness of a particular course of action (e.g., committing an evil deed to promote a greater good) on a scale from “very inappropriate” to “very appropriate.” Activity in one subset of brain regions, including anterior cingulate, insula, and superior temporal gyrus, was driven primarily by the participant’s emotional appraisal, while activity in another subset, including temporoparietal junction and dorsolateral prefrontal cortex, was driven by the participant’s utilitarian appraisal. Crucially, in the complex moral reasoning scenario in which the participant had to integrate both emotional and utilitarian factors to arrive at an overall moral judgment, the medial OFC’s activity was heightened. These results, along with others (e.g., Shenhav and Greene, [2014](#)), support the idea that the medial OFC may integrate different sources of information, such as emotional and utilitarian evaluations, that are relevant to overall moral judgments.

While researchers continue to debate the role of particular regions in complex moral reasoning tasks, a few key points are clear. First, there is no single brain region that categorically distinguishes between right and wrong. There is no “morality center” in the brain, just as there is no single center for language, emotion, vision, or memory. Second, existing evidence indicates that moral reasoning makes use of many of the same brain regions that are engaged in other complex reasoning and decision-making processes, such as the anterior cingulate cortex, dorsolateral prefrontal cortex, and OFC, as well as regions that encode emotional value. The fact that there is not a

uniquely moral region, or set of regions, makes evolutionary sense as well as being consistent with the empirical evidence. In the evolution of moral reasoning, it seems more plausible that already existing mechanisms that supported other kinds of decision making would be co-opted for moral reasoning, rather than that new brain regions would be developed for the sole purpose of moral reasoning.

In the end, can neuroscience help us to understand what we should do? Can neuroscience lead us to more moral behavior, to a society that is more fair and just? It is helpful here to distinguish between two kinds of knowledge, one of which we can call “harm to the brain” knowledge, and one of which we can call “neuroscience of moral reasoning” knowledge. Neuroscience can play a key role in informing moral judgments in “harm to the brain” scenarios. For example, neuroscience research on the effects of poverty and stress on the brain can help to better understand the harm done by societal systems or actions. As another example, research on the neural effects of repeated concussions in professional sports can help inform moral judgments about whether the rules of the sport, as presently played, adequately protect players (see In Focus box feature in [Chapter 16](#)). Research on neurocognitive function in states of unresponsive wakefulness can inform moral judgments about whether to take a patient off life support. In these examples, neuroscience provides information, albeit imperfect information, about the degree of harm done by an action or experience, and therefore can be an important element in evaluating the presence or extent of a moral wrong.

More controversial, though, is whether studies of the neural process of moral reasoning – studying which brain regions are activated when we try to discern right from wrong – can yield important information that helps to guide moral action, that is, to tell us what we, as individuals or as a society, should do. To put it more succinctly, knowing which brain regions are activated during moral reasoning may not have any bearing on whether the action being contemplated is right or wrong. The brain surely can and does engage in moral reasoning, and it is fascinating scientifically to unpack the mystery of how that happens in the wet tissue of the brain. But some philosophers have

argued that the neuroscience of moral reasoning is fundamentally irrelevant to what they refer to as the “normative question” of how we should reason about morally challenging scenarios (e.g., Berker, [2009](#); see also Greene, [2014](#)).

This debate pushes us to test the boundaries of cognitive neuroscience and to think more critically about what kinds of knowledge neuroscience can and cannot provide. In all cases considered in this chapter, as well as in many other topics covered in the book, we see that knowledge from neuroscience alone cannot definitively answer the most pressing questions for society. What it can do is to help us to appreciate human cognition, in both its capacities and its limitations, as part of the natural world, appropriately approached through the natural sciences. Scientific findings about the biology of cognition therefore can have implications for domains of human behavior such as education, law, and business. At the same time, the human brain both constructs the social world and is embedded within and influenced by it. The next generation of neuroscientists should actively consider the societal context in which the brain operates as well as the implications of neuroscience findings for society outside of the laboratory.

Summary

Public Perceptions of Neuroscience

- The general public has a strong interest in cognitive neuroscience because of its potential relevance to their own lives in both health and disease and its interface with such areas as education, law, business, and technology.
- Nonexperts in neuroscience may sometimes be misled by the “seductive allure” of findings about the brain, believing those findings to be more definitive than they really are. The need for critical thinking about neuroscience findings is paramount.

- Some studies suggest that brain images are especially influential in persuading people due to their vivid and seemingly concrete representation of complex mental processes.

Neuroscience and Education

- Cognitive neuroscience and education are natural partners, as neuroscience provides information about the neural basis of cognitive skills that are developed through education.
- Classroom demonstrations can help teachers and students learn about the brain and dispel “neuro-myths.” Learning about the brain in early years can promote children’s belief in their ability to get smarter if they try.
- Findings from cognitive neuroscience can illuminate specific areas of application in education, including development of skills in math, reading, and special needs instruction.
- One specific area of application is in understanding how the brain supports reading. Studies of the neural basis of dyslexia suggest that some of the neural differences associated with reading difficulties exist in pre-kindergarten years, before children begin learning to read. Neural measures taken during language tasks in preschoolers can predict which children will have more difficulty learning to read in the elementary school years, suggesting possible paths for early intervention.

Neuroscience and Social Inequality

- Children of lower socioeconomic status (SES) are at risk for lower academic achievement, which perpetuates inequality across generations. SES-related differences in cognitive skills during childhood, particularly in domains of

language and executive functions, are paralleled by structural and functional differences in brain development.

- Various causal explanations for the SES-related differences have been proposed, and they are not mutually exclusive. One explanation focuses on language use in the home, positing that enriched linguistic complexity in the home could account for the advantages in high-SES children at even a young age.
- Another possible causal path involves the influence of environmental stress on the developing brain. The stressors associated with poverty and other early adversities can affect the developing brain, particularly in frontal lobe regions that are important in both executive functions and language development.
- Interventions to address SES gaps in cognition and related aspects of brain development have focused both on school-based programs that attempt to strengthen children's self-control abilities and on family-based programs that include parent training in managing stress within the home environment.

Neuroscience and the Law

- Since law involves the societal regulation of human behavior, scientific findings about the neural basis of cognition and behavior, particularly in areas such as decision making, have potential implications for the law.
- The concept of evidence is different in the law versus science, accounting for some challenges when these disciplines intersect. Scientists think probabilistically and are expected to present all relevant evidence. Juries in the courtroom are often presented with selective evidence – that which attorneys opt to present in support of their case – and juries and judges are asked to make definitive rather than probabilistic judgments.
- One area in which neuroscience has affected legal thinking is in the area of adolescent brain development. Cognitive neuroscience studies indicate a

protracted course of brain development and cognitive abilities extending into late adolescence and early adulthood, particularly in areas of impulse control and decision making. These findings have implications for whether juveniles should be legally held to the same standards as adults.

- More generally, the issue of culpability – how responsible a person is for his or her actions – is an issue on which neuroscience evidence may be relevant. However, neuroscience evidence cannot at the present time be used to determine definitively whether a particular person has a “bad brain” that reduces culpability.
- Despite attempts to understand the neural mechanisms that contribute to the cognitive act of lying, neural measures of lie detection are not currently admissible as evidence in any US court. Difficulties in generalizing from controlled, artificial lab experiments of deception to real-world criminal contexts, combined with low accuracy of current brain-based lie detection methods, have been the key challenges in developing biological measures of deception that could be used in a courtroom.

Neuroscience and Performance Optimization

- Recent studies have focused on whether cognitive performance can be enhanced in healthy humans through biological manipulations. Enhancement in attention, vigilance, target detection, perceptual processing, learning, and memory could be relevant to high-performance occupations such as aviation and the military.
- Biological manipulations of cognitive performance have traditionally included pharmacological manipulations, such as stimulant drugs. More recently, research has focused on the potentially beneficial effects on cognition of magnetic or electrical stimulation, such as through TMS or tDCS. Some studies have found

evidence of improvements in attention, learning, and memory with such stimulation in healthy volunteers.

- Advances in computational methods have allowed for the real-time, instantaneous extraction of biofeedback in the form of EEG or fMRI signals. Such real-time data can be used to monitor a person's brain, for example to trigger warnings when drowsiness sets in, and to train people to control their brain activity in response to the real-time feedback, with potentially beneficial consequences for cognitive performance.
- Computational advances have also allowed real-time extraction of brain signals, such as from implanted electrodes and even noninvasive fMRI signals, to control external devices such as robotic arms or cursors on a computer. The ability of thoughts to control devices via neural measurement can even be extended to remote devices.
- Ethical issues arise when developing technology to improve the functioning and reach of the healthy brain. Both beneficial and malevolent consequences of technology must be considered. Ethical issues include possibility of implicit or explicit coercion, particularly in employment or military settings, and the perpetuation of social inequalities.

Neuroscience and the Marketplace

- “Neuro-marketing” refers to the use of neuroscience information, in addition to traditional surveys and focus groups, to aid marketers in connecting their products with consumers who are willing to buy them.
- While neuroscience information can give insight about neural mechanisms of the representation of value and willingness to pay, it is doubtful whether information gained about particular products would be worth the cost of neuroimaging to marketers.

- The orbitofrontal cortex (OFC) has been identified as most relevant to predicting a participant's likelihood of buying a product. The OFC's activity is altered by factors that affect a person's liking of a product (e.g., stated price) and is correlated with how much a person agrees to pay for a product.
- Neuroscience and the marketplace also intersect in the phenomenon of "brain branding," which refers to selling products by linking them to neural concepts (e.g., "brain training" programs for the elderly). Such branding, sometimes used even when no neuroscience evidence actually supports the product, takes advantage of the appeal of neuroscience to the general public.

The Neuroscience of Morality

- Morality most likely evolved in response to selective pressures derived from group living in social primates. Other primate species exhibit a rudimentary sense of fairness, in that they react negatively when treated less well than others.
- A sense of justice implies expecting fair treatment of others even when it contradicts self-interest. Neural mechanisms of empathy may serve as a basis for understanding the experiences of others, thereby promoting pro-social behavior. However, neural empathic responses are biased toward favored others, implying that empathy alone may not support the motivation for fairness toward all. The ability to take the cognitive perspective of another may be more relevant in supporting justice motivations.
- Reasoning about moral dilemmas recruits brain regions involved in complex decision making, such as anterior cingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex. Different subsets of brain regions are involved in representing the emotional value of a morally "good or bad" action versus the utilitarian value (costs and benefits to society), and medial OFC may serve to integrate these factors together into an overall moral judgment.

- Scientific data can help us to understand how various societal or individual actions may harm the brain, adding information that contributes to moral judgments about those actions. However, neuroscience studies of the process of reasoning during moral dilemmas cannot ultimately tell individuals or society how those moral dilemmas should be resolved.

Glossary

acceleration-deceleration injury

Diffuse damage created by a rapid acceleration of the head followed by a deceleration, in which the energy imparted to the brain causes it to move within the skull; main mechanism of damage in closed head injury.

acetylcholine

A neurotransmitter; plays an important role in overall arousal and excitability.

acetylcholinesterase

An enzyme that divides the neurotransmitter acetylcholine into its two constituent parts, choline and acetate.

action potential

Sequence of events occurring when a neuron fires: reversal of electrical charge to a peak of +40 mV (depolarization), retreat toward the baseline resting potential (repolarization), brief negative voltage (hyperpolarization), and return to resting potential.

action tremor

Staggered, jerky, and zigzag motion that occurs during the performance of an act, especially as the person zeroes in on a target.

activating-orienting model

Theory suggesting that an attentional set or bias can contribute to perceptual asymmetries. This model hypothesizes that engaging in a particular type of process causes greater activation in the hemisphere best suited to the task. The increased activity is thought to result in an attentional bias to the side of space contralateral to the more active hemisphere; thus, perceptual information on that side of space is more salient, allowing it to be processed better.

affective prosody

Communicates the emotional context or tone of an utterance.

agnosia

A modality-specific deficit in recognizing objects that occurs in the absence of major deficits in basic sensory processing.

agonists

Chemicals that mimic or facilitate the effect of a neurotransmitter on a target neuron.

agrammatic aphasia

Compromised ability to produce and comprehend the grammatical aspects of language; also called anterior aphasia.

agraphia

Loss of the ability to write, as a consequence of brain damage.

akinesia

Inability to initiate spontaneous movement.

alertness and arousal

The most basic levels of attention; conditions of responsiveness to the outside world.

alexia (acquired dyslexia)

Loss of the ability to read, as a consequence of brain damage.

allocentric reference frame

Category of reference frames that specify an object's location in relation to other objects, independent of one's own location.

alpha suppression

Decrease in the amount of alpha activity, used as an indicator of the degree of brain activation.

Alzheimer's disease (AD)

Dementia defined by a decline in memory and many other aspects of cognitive function, including at least one of the following: language, visuospatial skills, abstract thinking, motor performance, and judgment. Emotional dysfunction and personality changes are also typically observed.

amino acids

Smallest and most basic building blocks of proteins; act as the main excitatory and inhibitory neurotransmitters in the brain.

amnesia

Loss of memory that is global with regard to modality and material; inability to form most new long-term memories.

amyloid plaques

Deposits consisting of aluminum silicate and amyloid peptides (a build up or conglomeration of proteins), often including tau protein and apolipoprotein E; implicated in the genetic aspects of Alzheimer's disease and believed to cause vascular damage and neuronal cell loss.

anhedonia

Inability to find any pleasure in life; a characteristic of depression.

antagonists

Chemicals that oppose, block, or diminish the effect of a neurotransmitter on a target neuron.

anterior

Front; in front of.

anterior cingulate cortex (ACC)

Brain region located above the corpus callosum and below the cingulate sulcus, extending as far back as the central fissure; resides mainly in Brodmann areas 24 and 32, but also has portions in BA 25 and 33.

anterograde amnesia

Deficit in learning new information after the onset of amnesia.

anterograde disorientation

Inability to construct new representations of environments, although patients are still able to navigate successfully around previously learned environments.

anxious apprehension

Nervous anticipation of something bad that could happen in the future; worry.

anxious arousal

A state of bodily and cognitive hyperarousal characterized by physiological symptoms indicating activation of the sympathetic nervous system; panic.

apperceptive agnosia

A fundamental difficulty in forming a percept (a mental impression of something perceived by the senses); although sensory information is processed in a rudimentary

way, the data cannot be bound together to allow the person to perceive a meaningful whole.

approach-withdrawal model

Theory based on basic and rudimentary actions that organisms take in responding adaptively to the environment. Proposes that the left frontal region houses a system involved in approach behaviors and associated with (mostly positive) emotions that accompany approach behaviors; the right frontal region is posited to house a system involved in withdrawal behaviors and associated with (mostly negative) emotions that accompany withdrawal behaviors.

apraxia

Inability to link skilled motor movement to ideas or representations; inability to perform skilled, sequential, purposeful movement that cannot be accounted for by disruptions in more basic motor processes such as muscle weakness, abnormal posture or tone, or movement disorders; most common after damage to the left hemisphere.

aprosodia

Impairment or deficits in comprehension of prosody, resulting from brain damage.

aprosodic

All at one pitch; type of speech deficit observed after damage to anterior regions of the right hemisphere.

area MT

Brain region crucial to the ability to perceive and represent motion; also known as area V5.

Asperger syndrome

Describes individuals who meet the criteria for autism but are high-functioning in terms of their overall intelligence and language skills.

association area

An area of the brain where information from multiple modalities is processed.

associative agnosia

Disorder in which basic visual information can be integrated to form a meaningful perceptual whole, yet that particular perceptual whole cannot be linked to stored knowledge.

athetosis

Type of hyperkinesia characterized by involuntary writhing contractions and twisting of the body into abnormal postures.

attention

Selective process by which the brain chooses specific information for further processing; inherently limited by the amount of information the brain can process at any one time.

attention-deficit/hyperactivity disorder (ADHD)

A developmental disorder in which the affected child is either inattentive, hyperactive/impulsive, or both compared to the average child of the same age.

attentional set

Process that designates which information is task-relevant.

auditory agnosia

A specific inability to link basic auditory information to meaning; inability to recognize the meaning of sounds.

auditory-verbal working memory

Phonological store; memory of the contents of immediately preceding verbal utterances.

autism spectrum disorder

A pervasive developmental disorder associated with IQs that are significantly below average and profound cognitive, emotional, and social deficits.

autoreceptors

Receptors located on the presynaptic neuron that bind the same neurotransmitter as released by that neuron; regulate the responsiveness of cells by working as a negative feedback mechanism.

axon

Appendage of the neuron, along which information is carried from the cell body to the synaptic cleft.

axon hillock

Part of the neuron near the cell body where the action potential is first produced.

barbiturates

A class of CNS depressants, derived from barbituric acid, that reduce the activity of the CNS by binding to GABA receptors.

basal ganglia

A complex collection of subcortical nuclei located near the thalamus, consisting of the caudate nucleus, putamen, and nucleus accumbens (known collectively as the striatum); the globus pallidus (or pallidum); the substantia nigra; and the subthalamic nucleus. Important in motor control.

belt

Region of auditory cortex that surrounds (and receives most of its input from) the core; also receives some direct input from the medial geniculate.

benzodiazepines

Tranquilizing drugs that act by binding to GABA receptors.

bilateral

Both sides; two-sided.

binocular disparity

Discrepancy between the images seen by the two eyes; arises because the image that falls on each retina is slightly different, since the eyes are positioned in different locations. Acts as a cue for depth computation.

binocular rivalry

Oscillation of conscious perception that occurs when different stimuli are presented simultaneously to the left eye and the right eye.

blind spot

Area in the retina where there are no photoreceptors; the point at which all the ganglion cell fibers are gathered together in a bundle to exit the eye as the optic nerve.

blindsight

The retention of some visual capabilities without the conscious experience of seeing.

blood-brain barrier

Mechanism by which substances are prevented from reaching the brain; consists of tightly packed glial cells between blood vessels and neurons, which create a physical obstruction that keeps materials in the bloodstream from directly reaching the nervous system.

bottom-up attentional selection

Attention-directing schema in which some intrinsic aspect of the stimulus itself causes it to be attended or to receive priority in processing.

bradykinesia

Slowness of movement.

bradyphrenia

Slowing of thought processes; part of the cognitive compromise exhibited by individuals with Parkinson's disease.

brain-machine interface

A technological development that allows for direct connection between brain signaling and mechanical systems. An example is using recorded signals from motor cortex to control a robotic device.

Broca's aphasia

Syndrome in which a lesion to a specific region of the left hemisphere causes a loss of fluent speech even though the person's speech comprehension is relatively spared.

Brodmann map

Map (named after its creator) that divides the brain into distinct areas based on similarities in the laminar organization and nature of cells.

calcification

Accumulation of calcium; often accompanies transneuronal degeneration.

callosal apraxia

Disconnection syndrome that selectively disrupts the ability to perform movements or manipulate objects with the left hand in response to verbal commands; associated with damage to the corpus callosum.

callosal relay model

Concept that information received by the hemisphere less adept at a given task is transferred to the opposite hemisphere; this callosal transfer degrades the information and leads to poorer performance than if the information were received by the hemisphere more suited to the task.

caloric stimulation

Neglect-reducing technique in which water at least 7°C colder than body temperature is introduced into the ear canal, thereby inducing motion in the semicircular canals of the vestibular system and drawing attention to the neglected field or side of the body.

categorical spatial relations

Schema that specifies the position of one location relative to another in dichotomous categorical terms; may be specialized to the left hemisphere.

category-specific deficit

Inability to recognize or identify a certain category of objects even though the ability to recognize other categories of items in that same modality is retained.

caudal

Toward the back (in an animal, toward the tail).

caudate nucleus

Part of the basal ganglia.

cell body

The part of the cell containing the nucleus and other cellular apparatus responsible for manufacturing the proteins and enzymes that sustain cell functioning.

center-surround receptive field

Receptive-field structure of retinal ganglion cells and LGN cells; light stimulation in the center (or surround) excites cell firing, whereas light stimulation in the surround (or center) inhibits cell firing; helps to enhance contrast.

central executive

Theoretical construct in working memory; performs the mental work of (1) controlling slave subsystems that mediate the storage process and (2) forming strategies for using the information the subsystems contain.

central fissure

Split or chasm that separates each hemisphere of the brain in an anterior–posterior dimension; sometimes called the Rolandic fissure.

central nervous system (CNS)

Body system encompassing the brain and the spinal cord.

cerebellar ataxia

Difficulty in the coordination of movement that is observed after cerebellar damage.

cerebellum

Region at the back of the brain, located posterior to the medulla, that plays a major role in motor control through the regulation of muscle tone and guidance of motor activity; especially important in the coordination of muscle movement timing, the planning of movements, and the learning of motor skills.

cerebral achromatopsia

A clinical condition following brain damage in which a person loses the subjective experience of color vision due to cortical damage. People with this condition report that visual images appear in grayscale rather than color.

cerebral hemisphere

One of two physically separated halves of the cortex.

cerebrospinal fluid (CSF)

Fluid found between neurons and their bony encasements; similar in composition to blood plasma.

chorea

Type of hyperkinesia that produces uncontrollable, jerky movements such as twitching and abrupt jerking of the body.

cingulotomy

Surgical creation of bilateral lesions in the anterior cingulate.

closed head injury

Brain damage sustained when the head forcefully contacts another object, but no object penetrates the brain.

coarticulation

Differences in how the vocal muscles produce sounds (most notably vowels) depending on what precedes or follows them; phenomenon suggestive of motor planning.

cochlea

Spiral-shaped inner-ear structure containing the cells that translate sound energy into neural impulses; has a set of membranes that move in relation to one another when sound waves enter the ear.

cochlear nucleus

Area in the medulla where the auditory nerve synapses.

cognitive control

Process of guiding or controlling one's thoughts and actions. See also [executive functions](#).

cognitive neuroscience

Field of study comprised of investigations of all mental functions that are linked to neural processes.

cognitive reserve

The idea that people with greater mental capacity can sustain more damage to the brain before exhibiting symptoms.

cogwheel rigidity

Symptom of Parkinson's disease that causes limbs to move in specific, rigid steps, rather than moving smoothly; occurs because of increased muscle tone in the extensor and flexor muscles.

coincidence detectors

Cells in brainstem areas that take into account the different arrival times of a sound at the left and right ears; maximally stimulated when the signals from the right and left ears arrive at the cell simultaneously; codes for spatial location of the sound.

color constancy

A perceptual phenomenon in which the subjective experience of an object's color remains constant despite changes in the lighting conditions.

coma

State in which a person is unresponsive to and unaware of the outside world.

compensatory rehabilitation

Therapy for brain-damaged patients that aims to provide alternative strategies to achieve a particular goal.

complex cells

Type of striate cortex cells; respond best to certain line orientations and motion in a particular direction.

components

Characteristic portions of a scalp-recorded electrical waveform that have been linked to certain psychological processes.

computational models

Specific algorithms used in neural networks to simulate human mental functions; the basic component of most computational models is a “unit,” which exhibits behavior like an individual neuron.

computerized axial tomography (CAT, CT)

Process that uses X-rays to determine density of brain structures; in a CAT scan, dense tissue appears white and material with the least density appears black.

conduction aphasia

A disconnection syndrome characterized by inability to repeat what was just heard, although language comprehension and speech production are intact; caused by damage that severs the connection between Broca’s and Wernicke’s areas.

confirmation bias

A cognitive bias to interpret new information in a way that supports preexisting beliefs or opinions.

conformity

The tendency for people to shift their own opinions, perceptions, and judgments to align with those of other people.

connectionist networks

Computational model composed of interconnected layers of units that exhibit neuron-like behavior.

constructional apraxia

Disorder in which the spatial relations of items cannot be correctly manipulated; generally observed after right-hemisphere lesion and often associated with spatial processing difficulties and hemineglect.

constructional praxis

Ability to motorically produce or manipulate items so that they have a particular spatial relationship.

contention scheduling

One component of a two-component system that influences the choice of behavior; a cognitive system that enables relatively automatic processing, which has been developed over time through learning.

contextual fear conditioning

Conditioning in which a fear response is evoked by the context or environment in which an aversive stimulus had previously been presented.

contralateral

On the opposite side.

coordinate (metric) spatial relations

Schema that specifies the distance between two locations; may be specialized to the right hemisphere.

core

Area of auditory cortex that receives input from the medial geniculate nucleus; subdivided into areas A1 (primary auditory cortex) and regions anterior to A1,

referred to as the rostral and rostrottemporal fields.

corollary discharge

A signal to visual areas about upcoming eye movements, sent by motor-planning regions of the brain.

coronal

Planar view of the brain in which the brain is sliced ear to ear to separate the front from the back.

corpus callosum

Massive tract of more than 250 million nerve fibers that connects the hemispheres.

cortical blindness

Blindness caused by damage to primary visual cortex rather than by a problem in the eye or optic nerve.

cortical dementias

Declines in cognitive functioning that are primarily due to progressive, degenerative changes in cortical regions of the brain. Alzheimer's disease and frontotemporal dementia are the most common forms of cortical dementia.

cortical magnification factor

Describes the millimeters of cortical surface that are devoted to one degree of angle in the visual world.

cosmetic neurology

The use of neural intervention to improve cognition in healthy people.

countercoup (contrecoup) injury

Focal damage to the brain in a location opposite to an external impact (e.g., impact on front of head, but countercoup injury in posterior region). Countercoup injuries occur because the external impact causes the brain to move within the skull.

coup injury

Focal damage at the site of impact.

cranial nerves

The 12 major nerves originating in the brain; some are responsible for receipt of sensory information and motor control of the head, others are responsible for the neural control of internal organs.

crossed aphasia

Loss of speech ability (aphasia) resulting from a right-hemisphere lesion in a right-hander.

cross-modal plasticity

Brain reorganization in which cortex normally devoted to one sensory modality becomes able to respond to information supplied in another modality; may occur when a person loses input from an entire sensory modality.

crowding hypothesis

Theory regarding the phenomenon of later-emerging deficits following brain damage early in life; posits that the intact brain tissue takes on too many functions (by picking up the load of the damaged areas) to allow normal or optimal development of all functions.

cued recall

Memory test in which the person is given prompts to help him or her remember information that was previously encoded.

declarative memory system

Memory system, supported by the hippocampus, that allows particular information to be used flexibly in contexts not linked to the situation in which the information was acquired.

decomposition of movement

Strategy of moving one joint at a time in a serial manner to accomplish movement; used when multijoint coordination breaks down.

dedifferentiation

Effect of aging that causes the localization of function to become less defined with age.

deep brain stimulation (DBS)

Invasive experimental treatment for severe depression; involves implantation of electrodes deep within the brain to administer electrical current that modulates activity in the targeted brain region.

deep dyslexia (alexia)

Syndrome in which affected individuals show many of the deficits exhibited in phonological alexia (such as inability to read nonwords), and also show additional difficulties such as semantic paralexias, problems with reading abstract words, and trouble with reading small function words that serve as grammatical markers.

delay lines

Part of a brainstem system that assists in computing spatial location based on interaural time differences; signals representing incoming sounds travel along the delay lines, starting at different times from the left and right ears if the sound arrived at the two ears at different times.

delayed nonmatch-to-sample task

Test in which an animal is exposed to one of a large set of objects and, following a delay, is presented again with the object just viewed, together with another from the set of available objects; to receive a reward, the animal must select the object that was not previously presented. Reveals dissociation between long-term-memory deficit and fully functional working memory.

dementia

A debilitating syndrome involving a progressive loss of cognitive functions that interferes significantly with work or social activities; sometimes accompanied by personality changes.

dementia of the Alzheimer's type (DAT)

See [Alzheimer's disease](#).

dendritic tree

The part of the neuron that receives input from other cells.

dentate nucleus

Deep cerebellar nucleus to which the lateral zone projects.

developmental (congenital) prosopagnosia

Condition of being "face-blind" from birth, without any known brain damage.

developmental milestones

Changes that occur in an orderly fashion and at a particular age; include behavioral changes, acquisition of cognitive and motoric skills, and acquisition of other specific abilities.

dichaptic presentation

Method applied to investigate hemispheric differences in the somatosensory (touch) modality; the test subject (typically blindfolded) is asked to feel two items simultaneously, one in each hand, and then to identify these items in some manner.

dichotic presentation

Method for examining hemispheric differences in the auditory modality; different information is presented simultaneously to each ear so that each hemisphere receives two competing pieces of information, one from the ipsilateral ear and one from the contralateral ear.

diencephalon

Brain structure that contains the thalamus and hypothalamus.

diffusion tensor imaging (DTI)

Anatomical MRI method that can provide information not only about the structural integrity of brain regions, but also about the anatomical connectivity between different brain regions.

digit span task

Test in which a person must report back a sequence of digits read one at a time by the experimenter; reveals the person's working memory span.

dipole

A small region of electrical current with a relatively positive end and a relatively negative end.

direct access theory

Concept asserting that the hemisphere receiving sensory information processes it; when information is received by the hemisphere less suited to a task, performance is poorer than if the information is received by the hemisphere better suited to the task.

direct (lexical) route to reading

Method of reading in which print is directly associated with meaning, without the use of a phonological intermediary.

disconnection syndrome

A behavioral deficit that occurs when information carried by fibers of passage cannot be transmitted from one brain region to another.

discrimination

In the context of social cognition, behavior that is biased against a particular social group.

distal

Far.

disturbances of posture

Symptoms of Parkinson's disease that affect muscle groups throughout the body, causing difficulty in body position and locomotion, especially in movements that require postural adjustments or transitions.

divided attention

Occurs when attention must be split across tasks.

divided visual field technique

Studies that present information separately in each visual field, to take advantage of the neural arrangement by which information in the right visual field projects exclusively to the primary visual cortex of the left hemisphere and information presented in the left visual field projects exclusively to the primary visual cortex of the right hemisphere.

dopamine

A monoamine neurotransmitter (a catecholamine).

dorsal

Above or superior (in a four-legged animal, toward the animal's back).

dot probe task

Test in which the participant has to indicate the presence of a dot flashed on a screen; the dot is preceded by a pair of words, one of which is emotionally threatening. Faster response to the dot when it appears in the location of the threatening word, compared to the neutral word, demonstrates attentional bias to threatening information.

double dissociation

Research method that allows researchers to determine whether two cognitive functions are independent of one another.

double simultaneous stimulation

Condition in which identical stimuli are presented at the same time in both visual fields.

Down syndrome

Genetic disorder associated with severe retardation and characterized by a specific morphology of the body and face; caused by trisomy 21, a condition in which the 21st pair of chromosomes contains three chromosomes rather than the usual two.

dressing apraxia

Disorder in which the affected person has difficulty manipulating and orienting both clothes and his or her limbs so that clothes can be put on correctly; generally observed after right-hemisphere lesion and often associated with spatial processing difficulties and hemineglect.

dual-use dilemma

In the context of bioethics, the fact that many new technologies can be used for both beneficial and malevolent purposes.

dysarthria

Difficulty in speech output that is observed after cerebellar damage; characterized by slurred speech with sometime explosive variations in voice intensity.

dyslexia

Also called specific reading disability; a specific inability to learn to read at an age-appropriate level, despite adequate opportunity, training, and intelligence.

dysprosodic

With disordered intonation; type of speech deficit exhibited after damage to the left hemisphere.

dysthymia

A mild state of chronic depression lasting at least two years.

dystonia

A neurological disorder characterized by muscle contractions that result in twisting and repetitive movements and abnormal postures.

early-selection viewpoint

Theory regarding time frames of attentional stimulus processing; suggests that attentional selection occurs at an early stage of processing, before items are identified.

echolalia

Compulsive repetition of a sound or word.

edema

Swelling of tissue after trauma.

egocentric disorientation

Inability to represent the location of objects in relationship to the self; associated with damage to the posterior parietal region, either bilaterally or unilaterally in the right hemisphere.

egocentric reference frame

Category of reference frames that specify an object's location in relation to some aspect of the self.

electrical potential

The summed or superimposed signal of the postsynaptic electrical fields of similarly aligned neuronal dendrites, recorded at the scalp as a waveform; has a particular voltage and frequency.

electroencephalography (EEG)

Recordings of the brain's electrical activity; used clinically to detect aberrant activity, and used experimentally to detect psychological states associated with particular patterns of electrical activity.

emotion regulation

General term for attempts to manage the emotions that one experiences, so that they are socially appropriate and do not spiral out of control.

emotional Stroop task

Cognitive test in which the participant must identify the ink color of either emotionally threatening words or nonemotional words; slower color identification of

threatening words demonstrates attentional bias to threatening information in persons with anxiety disorders.

empathy

The ability to understand another person's feelings, and can include (1) emotional contagion that causes us to feel as others feel; (2) cognitive perspective-taking that allows us to understand another person's point of view; and (3) pro-social action, which involves behavior targeted to help another person in need.

endogenous components

Components that appear to be driven by internal cognitive states, independent of stimulus characteristics; typically occur later in the waveform.

environmental dependency syndrome

Disorder in which behavior is triggered by stimuli in the environment; involves automatic invocation of contention scheduling schemes because the supervisory attentional system has been lost.

enzymatic deactivation

Process in which an enzyme cleaves transmitter molecules so they become incapable of binding to the receptor.

enzyme

Any molecule that controls a chemical reaction, either by binding together two substances or by cleaving a substance into parts.

epilepsy

A disease in which seizure activity is recurrent but intermittent, diagnosed if two or more epileptic seizures have occurred.

epileptic seizures

Episodes in which synchronous activity of nerve cells increases so that a gigantic hyperpolarization of neurons spreads over a large area in an atypical and abnormal manner; during a seizure, neurons in the brain fire in an abnormal manner typified by great bursts or volleys, often called spikes. May be generalized or partial.

episodic memory

Autobiographical memories that are specific to one's particular experience; includes context about the time, space, etc.

error positivity (Pe)

An ERP signal that is thought to indicate awareness of an error; typically follows the error-related negativity (ERN) by about 200–300 ms.

error-related negativity (ERN)

An ERP signal that occurs approximately 100 ms after an error has been made.

estimate of premorbid functioning

A reasonable guess as to how well a person was performing before an injury.

event-related potentials (ERPs)

Recordings of brain activity that is linked to the occurrence of an event; derived from scalp-recorded EEG.

excitatory postsynaptic potential (EPSP)

Makes a cell's electrical charge slightly more positive by reducing the difference in electrical charge between the inside and the outside of the cell; this reduction brings the differential closer to the threshold value of -55 mV at which the cell will fire.

excitotoxicity

Excessive activity of receptors that can kill neurons by overstimulation (excite neurons to death).

executive functions

Abilities to plan actions to reach a goal, to use information flexibly, to think abstractly, and to make inferences (among other capabilities). See also [cognitive control](#).

exogenous components

Components linked to the physical characteristics of a stimulus; usually occur early in the waveform.

experience-dependent systems

Neural systems that vary across people and are based on the individuals' personal, unique experiences.

experience-expectant systems

Neural systems that respond to experiences universally present in normal development, relying upon external information essential for development but not specified in the genetic blueprint.

explicit memory system

Memory system that permits the conscious recollection of prior experiences and facts; lost in amnesia.

extended digit span

Test in which the same digit string is presented on each trial but with an additional digit added to extend the span; requires use of long-term storage in addition to working memory.

extinction

In fear conditioning paradigms, process by which acquired fears are later lost.

extrastriate body area

Neural module in the ventral visual processing stream (located in Brodmann area 18 in the occipitotemporal cortex); responds preferentially to human bodies and body parts.

fear conditioning

Method in which a stimulus comes to invoke fear because it is paired with an aversive event.

fetal alcohol spectrum disorders (FASD)

Intellectual disabilities caused by the mother's consumption of alcohol during pregnancy, and can range from severe (often called fetal alcohol syndrome) to less severe levels of disability.

fiber tract

Group of axons sent to the same place from different neurons.

fissure

Deep valley between brain convolutions.

forward model

Theory holding that the cerebellum helps to predict the sensory consequences of motor plans; argues that the cerebellum is involved in predictive movement.

fovea

Region in the center of the retina where cones are packed more densely.

fragile X syndrome

Inherited form of mental retardation in which a person's X chromosome has a section where a normally repeating sequence of genetic material occurs an unusually large number of times; reduces production of a protein called FMRP.

frames of reference

Concept that we can understand the spatial location of an object with respect to multiple reference points.

free recall

Memory test in which a person is asked to recall previously encoded information without any cues or prompts.

frontal eye field (FEF)

Portion of dorsal premotor regions; controls the voluntary execution of eye movements.

frontal lobe

Brain area in front of the central fissure.

frontotemporal dementia

Type of cortical dementia characterized by social-emotional dysfunction, with difficulty in modulating behavior; impulsivity and lack of inhibition; lack of concern for social norms and personal appearance; inappropriate sexual behaviors; and a preoccupation with repetitive or routinized behavior. Mood disorders and language/speech difficulties are also common.

functional brain connectivity

Patterns of brain connectivity deduced from observations of brain activation, such as determining whether the activity in two sets of brain regions increases and decreases over time in a similar manner.

functional connectivity

Communication or synchronization of activity between brain regions.

functional magnetic resonance imaging (fMRI)

Method most commonly used by cognitive neuroscientists to discern which areas of the brain are physiologically active; uses a variation of MRI techniques to measure changes related to blood flow and the metabolic changes in compounds used by different brain regions.

fundamental attribution error

An error in social cognition in which people tend to see their own actions as more socially constrained yet assume the actions of others are more attributable to their inherent personalities.

fusiform body area

Body-sensitive region located in the fusiform gyrus; responds preferentially to human bodies and body parts.

fusiform face area (FFA)

Neural module in the ventral visual processing stream; exhibits a greater response to faces than to other objects.

GABA

Gamma-aminobutyric acid; an amino acid that acts as an inhibitory neurotransmitter in the central nervous system.

ganglion cells

The retina's output layer of cells, whose axons form the optic nerve running between the retina and the brain.

gene-environment interactions

When a combination of specific environmental and genetic factors is necessary to bring about a certain behavior.

generalized anxiety disorder

A free-floating, chronic experience of anxiety that is not tied to any specific triggering event or object.

generalized (nonspecific) disorders

Clinical syndromes, including Alzheimer's disease, in which the breakdown of function is not restricted to one cognitive domain, but rather simultaneously affects multiple cognitive abilities.

geniculostriate pathway

Neural path from the LGN to visual cortex; enables the conscious experience of seeing.

Glasgow Coma Scale (GCS)

Tool for assessing level of consciousness, which evaluates three realms of functioning: visual responsiveness, motor capabilities, and verbal responsiveness; widely used in emergency rooms to classify the severity of damage in someone who has just sustained a head injury.

glia

Nervous system support cells.

gliosis

Process of phagocytosis and capillary formation that continues until only glial cells remain.

global aphasia

Inability to comprehend or produce language; associated with extensive left-hemisphere damage that typically includes both Wernicke's and Broca's areas and the area between them.

globus pallidus

Part of the basal ganglia.

glutamate

An amino acid that acts as the main excitatory neurotransmitter in the central nervous system.

Go/No-Go task

Test in which participants respond by pushing a button when certain visual stimuli appear (Go trials) and withholding response to other stimuli (No-Go); measures response inhibition.

grandmother cell theory

Theory that there is a particular cell in the ventral processing stream whose job is to fire when you see a particular object or person (such as your grandmother).

grapheme-to-phoneme correspondence rules

Rules whereby print is associated with sound.

grid cells

Located in the entorhinal cortex, grid cells have firing fields dispersed across the environment in a hexagonal grid, and are thought to help code an animal's location within a wider environmental cortex.

group studies

Research method in which patients with brain damage who have similar characteristics (e.g., lesions in similar areas) are studied as a group.

guilty knowledge test (GKT)

Used in forensic psychology to reveal knowledge that a participant, such as a criminal suspect, secretly holds. The GKT attempts to demonstrate differential behavioural or neural responses to information that only a guilty person would know.

gyrus

Convolution, or bump, of the brain formed by a giant sheath of neurons wrapped around other brain structures (plural: gyri).

habit learning

Category of skill learning; gradual and incremental learning that may not necessarily generalize to new exemplars.

hair cells

Cells in the inner ear that have tiny hairs called cilia sticking out of them; movement of the cilia in response to sound vibrations ultimately causes the cell to emit action potentials. The axons of the hair cells synapse on spiral ganglion cells, which make up the auditory nerve.

heading disorientation

A clinical syndrome, typically following damage to retrosplenial cortex, in which the patient has difficulty understanding his or her orientation (heading) within a spatial environment.

hemi-extinction

Condition in which information on one side of space is extinguished from consciousness (neglected).

hemi-inattention

Hemineglect.

hemineglect

Syndrome in which patients ignore, or do not pay attention to, information on one side of space (usually the left), and act as if that side of the world does not exist, despite having intact sensory and motor functioning.

hemiplegia

Paralysis of the side of the body contralateral to the site of brain damage.

hemispheric specialization

Difference in processing between the left and right hemispheres of the brain.

Heschl's gyrus

A superior portion of the posterior temporal lobe where the human primary auditory cortex is located.

higher-order thinking

Set of abilities involving complicated aspects of thought, such as being able to think in an abstract and conceptual rather than concrete manner, the ability to deduce rules or regularity, and the ability to be flexible and respond to novelty.

hippocampal system

Brain area where damage may result in amnesia or other memory-related disorders.

homonymous hemianopsia

Condition in which the entire occipital cortex of one hemisphere is damaged, so that no visual information can be detected in the contralateral visual field.

horizontal

Planar view in which the brain is sliced so that the top of the brain is separated from the bottom; also called axial or transverse.

human neuropsychology

Field of study that emphasizes examination of the changes in behavior as a result of brain trauma to understand mental processes in humans.

Huntington's disease

An inherited neurologic disease caused by degeneration of the striatum; produces abnormal movements, cognitive deficits (eventually dementia), and psychiatric symptoms.

hypercolumn

An organizational unit within primary visual cortex that includes orientation columns representing all possible line orientations and ocular dominance columns representing information from the left eye and right eye. Each hypercolumn represents only a specific region within retinotopic space.

hyper-complex cells

Type of striate cortex cells that fire most strongly in response to lines of certain lengths.

hyperkinesias

Involuntary, undesired movements.

hypofrontality

Hypoactivation (reduced activation) of frontal regions in people with schizophrenia.

Hypothalamic-Pituitary-Adrenal (HPA) axis

A system of hormonal control involving the hypothalamus, the pituitary gland, and the adrenal glands. The brain's hypothalamus releases corticotropin releasing factor (CRF), which stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH travels to the adrenal glands in the abdomen, and causes the adrenal glands to release the hormone cortisol, which then feeds back to further influence the hypothalamus and pituitary. The HPA axis is involved in regulating aspects of the stress response, as well as influencing other physiological functions such as digestion and energy use.

hypothalamus

Brain area controlling behaviors that help the body maintain equilibrium.

ideational apraxia

Also called conceptual apraxia; impairment of the ability to form an “idea” of a movement, so that a person cannot determine which actions are necessary and in what order they should occur.

ideomotor apraxia

A disconnection between the idea of movement and execution of the movement.

implicit memory system

Memory system that allows prior experience to affect behavior without conscious retrieval or awareness of the memory.

inference

The ability to “fill in the blanks” and make assumptions about material that is not explicitly stated (implied material).

inferior

Bottom; underneath; below.

inferior colliculus

One of two dorsal midbrain structures; acts as a relay point for auditory information and contributes to reflexive movements of the head and eyes in response to sound.

informational conformity

The reliance on other people’s opinions as a helpful source of information in ambiguous or uncertain situations.

inhibitory postsynaptic potential (IPSP)

Makes the inside of a cell slightly more negative than the outside, thus moving the cell further away from the threshold at which it will fire.

input phonological buffer

Holds auditory-verbal information received by the listener on-line while an utterance is being parsed.

intellectual disability

Occurs when a child fails to acquire intellectual abilities across most cognitive domains at a normal rate and manner and when the child has difficulties in adaptive functioning, such as self-care. Intellectual disability was previously referred to as mental retardation.

intention tremor

See [action tremor](#).

interaural intensity difference

Cue by which the brain deduces the spatial location of a sound source; depends on discrepancies in loudness between the ears.

interaural time difference

Cue by which the brain deduces the spatial location of a sound source; depends on discrepancies in time of sound arrival between the ears.

interference resolution

Ability to resolve conflict between competing information or distracting information that might interfere with performing a task.

interoception

Ability to perceive the internal state of the body.

intralaminar nucleus (of the thalamus)

Portion of the thalamus specifically implicated in the functions of alertness and wakefulness; acts by modulating the level of arousal of the cortex.

inversion effect

Phenomenon in which recognition (particularly of faces) is poorer when an object is turned upside down, because of the disruption of configural relationships.

ipsilateral

On the same side.

irregular words

Words that do not follow grapheme-to-phoneme correspondence rules and so are impossible to sound out correctly.

ischemia

Form of brain damage in which neurons die due to a lack of oxygen, most typically after blockage of a blood vessel in the brain.

Kennard principle

Theory that the earlier in life brain damage is sustained, the better the recovery.

landmark agnosia

Object-recognition deficit in which patients lose the ability to recognize certain landmarks that are usually used for navigation.

lateral

Toward the outside (of the brain).

lateral corticospinal tract

One of two major sets of pathways that link the brain to muscle. This tract, whose cell bodies are located mainly in primary motor cortex, crosses entirely from one side of the brain to the opposite side of the body in the medulla; thus, damage to this tract results in profound deficits in motor movement on the opposite side of the body, including the ability to reach, grasp, and manipulate objects.

lateral geniculate nucleus (LGN)

Complex layered structure in the thalamus that receives visual information from the retina and sends information on to the striate cortex.

lateral zone

Region of the cerebellar hemisphere that projects to the dentate nucleus.

lateralization of function

See [hemispheric specialization](#).

late-selection viewpoint

Theory regarding time frames of attentional processing; suggests that attentional selection occurs only after sensory processing is complete and items have been identified and categorized.

L-dopa

A metabolic precursor of dopamine; when taken orally, can reach the brain and stimulate pre- and postsynaptic dopaminergic receptors.

learning disability

Difficulty with acquiring cognitive skills in only one particular domain.

left visual field (LVF)

Area/information to the left of gaze fixation.

lesion method

Logical means of determining which regions of the brain are important for a given mental function: If damage to a particular brain region results in an inability to perform a specific mental function, scientists usually assume that the function must have depended on that brain region.

lexical agraphia

Syndrome in which the person can produce reasonable spelling, both manually and orally, for regular words or nonwords, but cannot spell irregular words.

limb apraxia

Disruption of the ability to use the limbs to manipulate items, to perform a complex series of movements, and/or to use motor movements in a symbolic or gestural way; usually produced by damage to left parietal or parietotemporal regions.

limbic system

A series of subcortical structures – including the amygdala, hypothalamus, cingulate cortex, anterior thalamus, mammillary body, and hippocampus – that sit below the neocortex; contributes to emotional and other functions.

localization of function

Concept that a processing subsystem uniquely dedicated to a single function is located in a specific region of brain tissue.

locked-in syndrome

Condition in which cortical function and awareness are normal but a brainstem injury prevents almost all motor output; locked-in patients are able to communicate using simple eye movements.

longitudinal fissure

Separates the right cerebral hemisphere from the left.

long-term potentiation (LTP)

Neuronal mechanism that allows processing of the conjunctions or co-occurrences of inputs, in which brief, patterned activation of particular pathways produces a stable increase in synaptic efficacy lasting for hours to weeks.

M and P ganglion cells

Retinal cells (also called parasol cells and midget cells, respectively) that form functional pathways with similarly named cells in the thalamus.

magnetic resonance imaging (MRI)

Technique that relies on the use of magnetic fields to distort the behavior of protons; information about how long the protons take to recover from this distortion is used to create an image of the anatomy of the brain.

magnetic resonance spectroscopy (MRS)

An MRI method that allows the concentration of certain biologically active substances, such as the neurotransmitters glutamate and GABA, to be determined in specific regions of brain tissue.

magnetoencephalography (MEG)

Method related to EEG that relies on the recording of magnetic potentials at the scalp (rather than electrical potentials) to index brain activity.

mammillary bodies

Parts of the hypothalamus; damage to these structures may result in amnesia.

mass action

Theory holding that all pieces of brain contribute to all functions; opposite of theory of localization of function.

material-specific memory disorders

Selective impairments of memory and/or recall; left-hemisphere damage impairs memory for verbal material; right-hemisphere damage impairs memory for nonverbal materials.

maturational lag hypothesis

Theory that children with specific learning disabilities are merely slower to mature than their peers, and that with time they will outgrow the problem.

medial

In the middle or center (of the brain).

medial dorsal nucleus (of the thalamus)

Portion of the thalamus specifically implicated in the functions of alertness and wakefulness; acts by modulating the level of arousal of the cortex.

medial geniculate nucleus

Structure in the thalamus that acts as a stopover point on the pathway relaying auditory information to the cortex.

medial pathway

One of two major sets of pathways that link the brain to muscles; involved in control of movements of the trunk and proximal limb muscles. This tract projects both contralaterally and ipsilaterally, and is mainly involved in the control of posture, as well as bilateral movements such as standing, bending, turning, and walking.

medulla

Section of the brain directly superior to the spinal cord; contains the cell bodies of most cranial nerves and controls many vital functions and reflexes.

memory consolidation

Process by which memories are strengthened to allow for long-term retention. Theoretically, the hippocampus aids in slowly binding together pieces of a memory trace in separate neocortical processors; once they are bound in this way, they can be retrieved without involvement of the hippocampal system.

mesocortical system

Dopaminergic subsystem with cell bodies located in the ventral tegmental area and projecting to much of the cortex; influences a variety of mental functions, notably working memory.

mesolimbic system

Dopaminergic subsystem with cell bodies in the ventral tegmental area, projecting to several parts of the limbic system; linked to reward-related behavior.

metacognition

The ability to reflect upon a cognitive process.

method of converging operations

Research technique of examining whether all the answers obtained from a set of interrelated experiments lead to the same conclusion.

midbrain

Brain region superior to the pons; contains the nuclei of some of the cranial nerves. Also contains the inferior and superior colliculi, which are important in orientation to stimuli in the auditory and visual modalities.

midline diencephalic region

Brain area, related to the hippocampus, where damage may result in amnesia.

midsagittal

Planar view in which the brain is cut down the middle, separating the left side from the right side.

mild cognitive impairment

Cognitive decline greater than is typical for a person's age, but not of sufficient severity to warrant a diagnosis of dementia; may be a precursor to Alzheimer's disease.

minimally conscious state

Condition in which a brain-damaged patient shows intermittent signs of awareness and purposeful action.

mirror neurons

Neurons, first identified within ventral premotor regions in the monkey, that fire not only when an organism performs a specific action but also when observing those actions being mimicked or mirrored by another organism.

mirror-reading task

Test in which word triplets are presented in mirror-image orientation, and the viewer reads them aloud as quickly and accurately as possible; determines whether a skill generalizes to new exemplars.

mirror-tracing task

Test in which the person must trace the outline of a figure by looking in a mirror.

mixed auditory agnosia

Disorder that affects the ability to attach meaning to both verbal and nonverbal sounds; however, the person can determine whether two sounds are identical or different and whether one sound is louder than the other.

mixed-variety dementias

Declines in cognitive functioning that are due to progressive, degenerative changes in both cortical and subcortical regions of the brain.

modality specific

Pertaining to or manifesting in only one of the senses.

monoamines

Neurotransmitters derived from amino acids that have undergone a chemical transformation via an enzymatic process; produced by neurons with cell bodies located subcortically and in the brainstem.

Morris water maze

Test of learning and memory of spatial relations in animals. A rat is placed in a circular tank filled with an opaque liquid that obscures a slightly submerged platform, which is positioned at a constant location relative to various visual cues outside the maze. Normal animals learn the position of the platform, and across trials there is a decrease in the time it takes them to swim to the platform.

motor plan

A motor plan is a plan of action for a sequence or series of movements. It is thought to be pre-programmed before the action is initiated.

motor program

A plan of action; an abstract representation of an intended movement.

motor unit

A motor neuron and the muscle fibers it innervates.

multiple-case-study approach

Research technique in which research findings are validated on a series of patients, each of whom is also treated as a single-case study. In this approach, data for each

person within each group are provided, so that researchers can determine the variability across people as well as the degree to which the overall group average typifies the behavior of individuals within the group.

multiple-resource theory

Suggests that a limited set of distinct attentional resource pools may exist, each of which can be applied only to certain types of processes.

multiple sclerosis (MS)

Neurological disease of nontraumatic origin in which demyelination leads to axonal degeneration and interferes with neural transmission. Symptoms may include weakness in the extremities, difficulty in some aspect of sensory processing, and changes in cognition, mood, and personality; however, the course and effects of the disease vary.

multi-voxel pattern analysis (MVPA)

An analysis method that examines the pattern of brain activity across a set of voxels rather than just examining how much activity is observed in any given voxel.

myelin

Fatty sheath that insulates the axon.

narrative

The ability to construct or understand a story line.

necrosis

Cell death.

negative symptoms

Absence of normal behavior in schizophrenia (e.g., catatonia, flat affect).

neologisms

Made-up words that follow the rules for combining sounds in the language, yet are not real words.

neurodevelopmental hypothesis

Theory regarding the etiology of schizophrenia. Argues that neural functions are subtly altered early in life, leaving the person with a vulnerable neural organization that may lead to emergence of the disorder after puberty or at the onset of young adulthood.

neurofibrillary tangles

Twisted pairs of helical filaments found within the neuron; thought to disrupt a neuron's structural matrix.

neurogenesis

The generation of new nerve cells.

neuro-marketing

A term typically used to describe the use of neuroscience information for purposes of marketing.

neuromuscular junction

Synapse between a neuron and muscle fibers; is larger and has a more specialized structure than a typical synapse.

neurons

Nervous system cells that carry information from one place to another by means of a combination of electrical and chemical signals.

neuropsychological assessment

Evaluation performed to determine the degree to which damage to the central nervous system may have compromised a person's cognitive, behavioral, and emotional functioning.

neuropsychological test battery

Multiple tests used to detect any type of brain dysfunction of either neurological or psychiatric origin; most common is the Halstead-Reitan battery.

neurotransmitter

Molecules that are released from the presynaptic neuron and received by the postsynaptic neuron; enable transmission of signals.

neurulation

Formation of a tube, early in fetal development, that later becomes the spinal cord and brain.

nigrostriatal system

Dopaminergic subsystem with cell bodies located in the substantia nigra and projecting to the neostriatum (the basal ganglia); regulates the selection, initiation, and cessation of motor behaviors.

nodes of Ranvier

Gaps between myelinated sections of an axon.

nonmatch-to-sample paradigm

Test procedure in which the participant must choose the item that does not match the previously shown sample object; normal performance requires an ability to discriminate between the two shapes.

nonverbal auditory agnosia

Disorder characterized by inability to attach meaning to nonverbal sounds, although ability to attach meaning to words remains intact.

noradrenaline/norepinephrine

A monoamine neurotransmitter (a catecholamine).

nuclei

Distinct groups of neurons whose cell bodies are all situated in the same region.

nucleus accumbens

Part of the basal ganglia; a cluster of cells in the basal forebrain (also called the ventral striatum). One of the brain areas where electrical stimulation is most rewarding.

object-based neglect

Condition in which the individual neglects the left half of the stimulus (typically an object or word) regardless of the position of the stimulus in space.

object-based viewpoint of attention

Theory that top-down signals cause attention to be directed on the basis of particular objects.

object-centered neglect

Condition in which the patient ignores half of an object regardless of how that object is displayed or oriented.

obsessive-compulsive disorder (OCD)

Syndrome in which the afflicted person has obsessive thoughts about harm and copes with that anxiety by engaging in repeated, compulsive actions intended to ward off a negative outcome.

occipital lobe

Brain region behind the parieto-occipital sulcus.

ocular dominance columns

Columns of cells in primary visual cortex, in which all the cells in the column respond to input from only one eye (either the left or the right eye).

olfactory bulb

A thin strand of neural tissue located directly below the frontal lobe; one of two bulbs (one in each hemisphere) that receive and project sensory information about smells.

oligodendrocytes

Glial cells that produce the insulating myelin sheath for a neuron.

optic ataxia

A failure in visually guided reaching; caused by superior parietal lobe damage.

optic chiasm

Crossover point where some information from the left eye is transmitted to the right side of the brain, and vice versa; place where information from the inside half of each retina crosses the midline of the body and projects to the contralateral lateral geniculate.

optic flow

The pattern of movement of images on the retina as one moves actively through an environment.

optic nerve

The optic nerve carries visual information from the eye to the brain. It is formed by the axons of the retinal ganglion cells, and it terminates in the superior colliculus and the lateral geniculate nucleus.

optical imaging

Imaging technique in which a laser source of near-infrared light is positioned on the scalp, with detectors composed of optic fiber bundles located a few centimeters away from the light source. The detectors sense how the path of light is altered, either through absorption or scattering, as it traverses brain tissue. Can provide cognitive neuroscientists with simultaneous information about the source and time course of neural activity.

optimal feedback control

Viewpoint (derived from computational models) that conceptualizes the motor regions of the brain working together as a circuit to reach a goal, which can met by a number of different movement options.

oral (buccofacial) apraxia

Difficulty in performing voluntary movements with the muscles of the tongue, lips, cheek, and larynx, although automatic movements are usually preserved; usually produced by frontotemporal lesion.

orbitofrontal cortex (OFC)

Brain region most implicated in integrating emotion and decision making; includes regions that directly overlie the eye orbits and areas that extend into the medial wall of the frontal lobes (ventromedial prefrontal cortex).

orientation columns

Columns of cells in primary visual cortex, in which all the cells in the column respond best to visual images of line segments oriented in a particular direction.

output phonological buffer

Holds the phonological code on-line as a speaker is preparing his or her own utterance.

paired-associate learning

Memory-task format in which the participant must learn to associate pairs of items with one another; emphasizes declarative memory and engages hippocampal regions.

panic disorder

Repeated attacks with sensations of extreme bodily hyperarousal, dizziness, shortness of breath, elevated heart rate, and sense of losing control; may be associated with fear of specific situations.

parabelt

Region of auditory cortex that surrounds the belt; receives input from the belt and the medial geniculate.

parahippocampal place area (PPA)

A region within parahippocampal cortex, in the medial temporal lobe, whose activity increases when participants view familiar places or landmarks.

paraphasias

Errors in producing specific words.

parietal lobe

Brain region directly behind the central fissure and above the Sylvian fissure.

Parkinson's disease

Disease resulting from damage to the cells of the substantia nigra, which stop producing the neurotransmitter dopamine; may be caused by genetic predisposition, toxins, trauma, inflammation, or viral infection.

Parkinsonian mask

An expressionless face that is a prominent symptom of Parkinson's disease; may reflect a dampening of both movements and emotional responsiveness.

pattern cells

Pattern separation is a computational process whereby a set of inputs are transformed into a set of outputs that are less similar than the original inputs.

pattern completion

Process in which interaction of the hippocampal system with neocortical storage sites may allow one piece of information to be used to reconstitute a whole memory (essentially, to reactivate long-term memories).

perception

A term usually used to refer to how the brain organizes sensory information into meaningful representations of objects and scenes, such as visual objects or recognizable sounds.

perceptual asymmetries

Differences in performance between hemispheres observed through asymmetry in the perception of information depending on which part of the sensory system is stimulated; allows researchers to assume that the favored hemisphere is specialized for processing that type of information.

peripheral nervous system

All neural tissue beyond the central nervous system, such as neurons that receive sensory information from or send information to muscles, and neurons that relay information to or from the spinal cord or the brain.

perseverate

Perform a behavior repeatedly.

perseveration

Behavior of repeating the same action (or thought) over and over again.

phobias

Irrational fears, centered on specific objects or situations, that interfere with normal functioning.

phonemic paraphasia

Error in which the substituted word sounds similar to that of the intended word.

phonological agraphia

Syndrome in which the person can manually or orally spell regular and irregular words in dictation but performs poorly with nonwords.

phonological awareness

Ability to process the critical acoustic parameters, such as voicing, that distinguish between phonemes; involves ability to link a particular letter to a particular sound and to parse words into their constituent phonemes.

phonological dyslexia (alexia)

Syndrome in which the affected person does not have an association between the visual form of words and meaning; due to a disrupted phonological route but an intact direct route, the person can read previously learned words (whether regular or irregular), but cannot read nonwords or unfamiliar words.

phonological (nonlexical) route to reading

Method of reading that links information in a visual linguistic format to meaning by identifying each letter and blending the sounds to produce a word; word recognition occurs because the sound pattern is associated with the concept that the word represents.

phonological processing

The linking of a particular letter to a particular sound and being able to parse words into their constituent phonemes.

phonology

Study of the sounds that compose a language and the rules that govern their combination.

photoreceptors

Sensory receptors in the eye, called rods and cones, which contain pigments that absorb light.

place fields

Particular places in the environment to which hippocampal neurons fire preferentially.

place of articulation

The location in the vocal tract where airflow is obstructed during normal speech/sound production.

planum temporale

Temporal plane; the region at the end of the Sylvian fissure in the temporal lobe.

plasticity

Malleability; quality of dynamically changing in response to environmental and developmental factors or in response to damage.

pons

Multifunctional brain area directly superior to the medulla and anterior to the cerebellum. Contains the superior olive (which relays auditory information from the ear to the brain); acts as the main connective bridge from the rest of the brain to the

cerebellum; is the point of synapse of some cranial nerves; and acts to control certain types of eye movements and vestibular functions.

population coding

Theory that the pattern of activity across a large population of cells codes for individual objects.

positive symptoms

In schizophrenia, excesses or distortions in normal behavior (e.g., delusions, hallucinations).

positron emission tomography (PET)

Imaging method that uses a radioactive agent to trace and determine the brain's metabolic activity.

posterior

Back; behind.

post-error slowing

Behavior typically observed after errors on tests; people are more cautious and respond more slowly on the next trial after an error.

posttraumatic amnesia

A loss of memory following a traumatic brain injury.

posttraumatic stress disorder (PTSD)

Disorder caused by a deeply traumatic or life-threatening experience. Symptoms include vivid, intrusive recollections of the traumatic situation; avoidance of situations related to the traumatic experience; chronically elevated bodily arousal; feelings of survivor guilt; and suicidal thoughts.

praxis

System responsible for production of skilled motor movement; probably requires a wide variety of brain regions, including the parietal, prefrontal, motor, and subcortical regions, each contributing in a different manner to the planning, retrieval, and/or implementation of motor action plans.

prejudice

A negative attitude about a particular social group.

premotor area

Located on the lateral surface of the brain just in front of primary motor cortex; sends commands to the primary motor area.

premotor cortex

The area directly in front of primary motor cortex on the lateral surface of the brain; involved in programming the type of motor action to be taken, such as a pincher grasp rather than a whole hand grasp.

primal sketch

Visual system construct of features in the visual world, which distinguishes dark from light regions and groups them together.

primary motor cortex

Cortical region that is the final exit point for neurons responsible for fine motor control of the body's muscles.

primary sensory cortex

Cortical region that initially receives information about a particular sensory modality.

procedural memory system

Supports memory of “how” things should be done, allowing for the acquisition and expression of skill; learning in this system is probabilistic, integrating information across events rather than storing each event separately.

prodromal

A stage of disease when early signs may be evident but the disease is not fully manifest yet.

propositional prosody

Communicates lexical or semantic information.

proprioception

Perception of the position of body parts and their movements.

prosody

The intonation pattern, or sound envelope, of an utterance; tone of voice in which a phrase is spoken.

prosopagnosia

A selective inability to recognize the identity of faces (although the ability to correctly identify other objects in the visual modality is retained).

proximal

Near.

psychic blindness

Disconnection between the ability to process the sensory properties of objects and the understanding of the affective properties of those same objects.

psychological inertia

Consequence of executive dysfunction; persons with this symptom are poor at starting an action or a behavior, but once engaged in it, they have great difficulty stopping it.

pulse sequence

An oscillating magnetic field that creates a perturbation in the static field.

pulvinar (of the thalamus)

Thalamic structure that plays a role in attention and the filtering-out of distracting information.

pure-word deafness

See [verbal auditory agnosia](#).

putamen

Part of the basal ganglia.

pyramidal cell

Specific type of myelinated neuron; involved in controlling muscle movement.

quadrantopsia

Disorder in which one quadrant of the visual world is lost; caused by damage to a dorsal or ventral portion of the occipital cortex in one hemisphere.

receiver coil

A radio-frequency apparatus that records the time it takes for protons perturbed in an MRI to revert to their original state.

receptive field

That specific region of visual space to which a particular cell responds or is sensitive; a part of visual space in which light will affect the cell's firing rate.

receptors

Specially configured proteins, embedded within the postsynaptic membrane, that create binding sites for neurotransmitter.

recognition memory

Test paradigm in which a person views a list of items to remember, and then later is shown both old and new items and asked which of them were previously seen.

regeneration

Process of creation of new cells, both neurons and glia; also involves sprouting of new axons, connection of regions that were not previously connected, and formation of new synapses.

reinforcement contingency

The degree to which a reward or punishment is associated with a particular stimulus or action.

relational learning

Hippocampal memory system that supports learning (whether conscious or unconscious) occurring in tasks or situations where performance depends on acquiring memory for the relations among items, especially items associated only arbitrarily.

relay center

A brain region whose neurons receive information from one area of the brain and then go on to synapse elsewhere in the brain; often a site for reorganization of information.

reorganization

Changes in the brain that occur when one cortical region “takes over” the functions of another damaged or dysfunctional region.

repetition priming

Enhancement or biasing of performance as a result of previous exposure to an item; major category of preserved learning and memory in amnesia.

repetitive transcranial magnetic stimulation (rTMS)

Experimental treatment for depression in which repetitive magnetic pulses are applied to the brain from a generator held outside the scalp.

response inhibition

Ability to override or interrupt ongoing processing, or to abort inappropriate responses.

resting potential

The difference in electrical charge between the inside and outside of the neuron; typically about -70 millivolts.

resting state networks

Networks of brain regions whose activity rises and falls in a similar pattern over time while the brain is at rest, generally assessed when people are simply looking at a fixation cross or lying in the magnet with their eyes closed.

reticular activating system (RAS)

A set of brainstem neurons that receives input from the cranial nerves and projects diffusely to many other regions of the brain; relies on the excitatory neurotransmitter glutamate. Important for overall arousal and attention, and for regulation of sleep-wake cycles.

reticular nucleus (of the thalamus)

Portion of the thalamus specifically implicated in the functions of alertness and wakefulness; acts by modulating the level of arousal of the cortex.

retina

Structure at the back of the eye that registers light and processes visual information before sending it on to the brain.

retinotopic map

Characteristic of some areas of the visual system (e.g., in LGN or striate cortex), in which visual information is laid out spatially like the retina itself, such that neighboring cells respond to light stimulation at neighboring regions on the retina.

retrograde amnesia

Memory impairment for information that was acquired prior to the event that caused the amnesia; a deficit stretching back in time to some point before the onset of amnesia.

reuptake

Rapid removal of neurotransmitter back into the terminal bouton by special transporter molecules embedded in the presynaptic membrane.

reversal learning

Ability to change behavior when contingencies change; ability to reverse a previously learned correct response.

Ribot's Law

Rule relating to the amount of time over which retrograde amnesias extend: generally, there is greater compromise of more recent memories than of more remote memories.

right visual field (RVF)

Area/information to the right of gaze fixation.

rostral

Toward the front (in an animal, toward the head).

rotary pursuit

Task in which a person has to track a circularly moving target; reveals ability to learn a perceptual-motor skill.

saccade

An eye movement in which the eyes, rather than moving smoothly across space, jump from one position to the next with no processing of the intervening visual information.

sagittal

Planar view in which the brain is cut so that the left side is separated from the right side.

scotomas

Blind spots; particular regions of the visual field in which light-dark contrast cannot be detected. Caused by damage to small portions of the visual cortex.

selective attention

Involves the choice of information essential to a task; often conceptualized as a filtering process that allows homing in on critical information from the vast amount of information available. This selection process can be performed on incoming sensory information, on information being kept “in mind,” or on the set of possible responses.

self-ordered pointing task

Test of sequencing ability. The person is shown an array of items laid out on a page, followed by another page with those same items in a different arrangement, etc. The participant must point to a unique item on each successive page, which requires keeping track of which items were previously selected.

semantic dementia

Disorder in which the affected person progressively loses the ability to retain semantic information.

semantic memory

Knowledge that allows the formation and retention of facts, concepts, categories, and word meaning and retention of information about ourselves and the people we know – all of which are expressed across many different contexts.

semantic paralexias

Reading errors in which a word is misread as a word with a related meaning.

semantic paraphasia

Error in which the substituted word has a meaning similar to that of the intended word.

semantics

The meaning of language.

sensation

A term usually used to describe the registration and initial encoding of sensory information, such as light and sound waves.

sensitive period

Specific time during development when the organism is particularly responsive (sensitive) to certain external stimuli.

sensory gating

Pattern in which the neural response to the second of two successive auditory tones or clicks is less than the response to the first stimulus.

sequencing

One of the basic processes involved in reaching a goal; ability to determine what steps to take to attain the goal, and the order in which those steps must be taken.

serotonin

A monoamine neurotransmitter (an indolamine).

serotonin transporter gene

Gene that codes for the serotonin reuptake protein, which takes the neurotransmitter serotonin from the synapse back up into the presynaptic cell.

simple cells

Type of striate cortex cells; responsive to bars of light oriented in particular ways.

simulation

Mimicking or acting like another person in order to comprehend that person's mental state.

single-case studies

Research method in which a single patient with brain damage is studied intensively with a variety of neuropsychological tests.

single photon emission computed tomography (SPECT)

A method that uses a radioactive isotope of specific elements or compounds to determine brain activity. The spatial resolution of this method is less precise than positron emission tomography.

skill learning

The acquisition – usually gradually and incrementally through repetition – of motor, perceptual, or cognitive operations or procedures that aid performance.

social brain hypothesis

A hypothesis that posits that the primate brain evolved to be disproportionately large, compared to other species, in order to support processes of social cognition that are necessary for successful group living.

social influence

The general idea that our thoughts, attitudes, beliefs, and actions are influenced by other people.

social norms

Written and unwritten rules that govern social behaviour, such as codified laws or implicit rules of etiquette.

somatosensory agnosia

Condition in which a person is unable to recognize an item by touch but can recognize the object in other modalities.

source memory

The ability to recall or remember the specific circumstances or context in which particular information was learned.

space-based viewpoint of attention

Theory that top-down signals cause attention to be directed on the basis of locations in space.

sparse coding

Theory that a small but specific group of cells responds to the presence of a given object.

spinal cord

Portion of the nervous system through which many sensory neurons relay information to the brain, and through which motor commands from the brain are sent to the

muscles.

split-brain procedure

Surgical procedure in which the corpus callosum – the primary route by which the left and right cerebral hemispheres interact – is severed, thereby splitting the brain in half; also sometimes referred to as commissurotomy.

static magnetic field

A constant magnetic field; MRI machines are classified by the strength of this field.

stereotype threat

A phenomenon in which activation of a stereotype can lead to underperformance by a member of a stereotyped group.

stereotyping

The tendency to assume that certain characteristics are universally true of group members. For example, we may hold a stereotype that women are nurturing or that Asians are good at math.

striate cortex

Primary visual cortex; contains a map that is retinotopically organized.

subcortical dementias

Declines in cognitive functioning that are primarily due to progressive, degenerative changes in subcortical regions of the brain, such as the basal ganglia. Examples of subcortical dementias are Parkinson's and Huntington's diseases.

subsequent memory effect

Effect in which subsequently remembered items are associated with greater brain activity at encoding than items that are not subsequently remembered.

substantia nigra

Part of the basal ganglia.

subthalamic nucleus

Part of the basal ganglia.

sulcus

Valley between brain convolutions (plural: sulci).

superior

Top; above.

superior colliculus

One of two dorsal midbrain structures; allows orientation of eyes toward large moving objects in the periphery, so that the object falls in the center of vision. Also permits one to move the focus of visual attention from one position or object to another.

superior olivary nucleus

Structure in the medulla to which the cochlear nucleus relays auditory information.

supervisory attentional system

One component of a two-component system that influences the choice of behavior; cognitive system required to effortfully direct attention and guide action through decision processes. Active only in certain situations: when no preexisting processing schemes are available, as occurs in novel situations; when the task is technically difficult; when problem solving is required; and when certain typical response tendencies must be overridden.

supplementary motor area (SMA)

A specific brain region that transmits information about a motor program to other brain regions, eventually allowing activation of the specific muscles required to execute the program.

supplementary motor complex (SMC)

One of the main regions of the brain that plays a role in planning, preparing, and initiating movements. Located mainly on the medial surface of the brain, and is composed of the more posteriorly located supplementary motor area, the more anteriorly located pre-SMA, and the supplementary eye field.

surface dyslexia (alexia)

Syndrome in which the affected person cannot link the visual form of a word directly to meaning; involves disruption in the direct route but not the phonological route.

switch cost

Time (or other resources) needed to change the current task set.

Sylvian (lateral) fissure

Separates each hemisphere of the brain in the dorsal-ventral dimension; sometimes called the fissure of Sylvius.

synapse

Region of contact between the neuron containing the terminal bouton, the synaptic cleft, and the postsynaptic region.

synaptic vesicles

Small balloon-like structures in and on the neuron that are filled with neurotransmitter.

synaptogenesis

Creation of connections (synapses) that neurons make with other neurons; increases dramatically after birth.

syntax

The rules of grammar.

tactile agnosia

See [somatosensory agnosia](#).

tactile asymbolia

Disorder in which a person can form a percept from tactile information, but cannot link that percept to its symbolic meaning.

tectopulvinar path

Neural pathway from the retina to the superior colliculus to the pulvinar nucleus; allows quick orientation to important visual information; especially sensitive to motion and appearance of novel objects in the visual periphery.

telegraphic speech

Nonfluent speech in which sentences are structured like a telegram or text message; uses primarily content words, such as nouns and verbs, and omits function words (such as conjunctions and prepositions) and word endings.

temporal gradient

Effect of amnesia in which there is greater compromise of more recent memories than more remote memories.

temporal lobe

Brain area below the Sylvian fissure; plays an important role in memory, emotion, and auditory perception.

temporally limited retrograde amnesia

Memory loss that extends back a certain amount of time; often 60 minutes before injury, but possibly extending to years or decades earlier.

thalamus

Part of the diencephalon; a large relay center for almost all sensory information coming into the cortex and almost all motor information leaving it.

theory of mind

Theory that assumes that we have a cognitive representation of other people's mental states, including their feelings and their knowledge.

three-dimensional (3-D) representation

Abstract, viewpoint-independent mental construct of an object.

tics

Repetitive involuntary movements of a compulsive nature that wax and wane in severity.

tonotopic

Organized with regard to the frequency of a tone or sound.

tonotopic map

Area in the brain (e.g., in auditory cortex) that organizes information according to sound frequency.

top-down attentional selection

Attention-directing schema in which the individual determines how to direct attention based on task goals, instructions, or higher-level decisions.

Tourette's syndrome

A relatively rare disorder that manifests as a variety of vocal and motor tics; appears in childhood.

Tower of London task

Test of planning and sequencing; the task requires the person to move a set of balls, one at a time, from an initial position on prongs to a target configuration in as few moves as possible while keeping in mind the constraints imposed by the height of each prong.

tractography

Method that builds on diffusion tensor information to ascertain information about probable white-matter tracts in the brain.

transcranial magnetic stimulation (TMS)

Methodology by which researchers modulate or change brain activity in neurologically intact people; a pulsed magnetic field, created by a coil or series of coils placed on the scalp, induces an electrical field that alters the pattern of brain activity in the underlying tissue.

transneuronal degeneration

Cell loss and death that extends past the actual site of damage to more distal neurons.

traumatic brain injury (TBI)

A sudden injury to the brain from an external force, such as a closed head injury from a car accident or a penetrating head injury from a missile wound.

tremors

Repetitive rhythmic motions that result from oscillatory movement of agonist and antagonist muscles.

tuning curve

Graph that shows an auditory system cell's sensitivity to sounds of different frequencies.

unilateral

One side; one-sided.

unresponsive wakefulness syndrome (UWS)

An altered state of conscious awareness following severe brain injury in which the patient shows signs of wakefulness, such as eyes opening, but is completely unresponsive to stimulation and does not communicate in any way. This condition was previously referred to as a vegetative state.

vagus nerve stimulation (VNS)

Experimental treatment for depression in which a device containing stimulating electrodes is implanted in the upper chest, near the collarbone, where it can stimulate the vagus nerve before it enters the brain.

vascular dementia

Formerly known as multi-infarct dementia; results from the cumulative effects of many small strokes that tend to create both cortical and subcortical lesions. Patients usually demonstrate similar dysfunctions as observed in Alzheimer's disease.

ventral

Below or inferior (in a four-legged animal, toward the animal's stomach).

ventral visual processing stream

Consists of the areas of the occipital, occipitotemporal, and temporal regions that are devoted to processing visual stimuli; characteristics of cells in these areas seem to be especially adaptive for object recognition.

ventricles

A network of interconnected cavities within the brain that are filled with cerebrospinal fluid.

verbal auditory agnosia

Disorder in which words cannot be understood, although the ability to attach meaning to nonverbal sounds is intact; linguistic processing ability remains otherwise normal.

viewer-centered representation

Model of visual recognition in which stored representations of objects are specific to certain viewpoints of those objects.

vigilance

Sustained attention; the ability to maintain alertness continuously over time.

visual agnosia

An inability to recognize objects in the visual modality that cannot be explained by other causes.

visual-verbal working memory

Ability to hold visual-verbal information on-line during reading.

visual word form area (VWFA)

A region of the ventral temporal lobe that is especially activated by visually presented words or pronounceable letter strings.

visuospatial scratch pad

Ability to hold nonverbal visual information while performing perceptual analyses of a stimulus array.

voicing

The timing between the release of air for a stop consonant and the vibration of the vocal cords.

Wada technique

Procedure used to determine which hemisphere is responsible for speech output in patients about to undergo tissue removal to control epileptic seizures; a sedative is introduced into the carotid artery serving one hemisphere, and the experimenter observes whether disruptions in speech occur.

Wernicke's aphasia

Syndrome in which there is disrupted speech comprehension along with fluent (but nonsensical) speech output; speech output occurs without hesitation, sounds are well formed, and all parts of speech are present, but output is a jumble of words, often referred to as a word salad.

Wisconsin Card Sorting Test (WCST)

Classic neuropsychological test used to examine task-switching. The participant is to sort a stack of cards into four piles based either on the color, number, or shape of the items on the card. No explicit criteria for sorting are given, but as the participant places each card onto one of the four piles, the experimenter indicates whether the response is correct or incorrect. From the experimenter's feedback, the participant must deduce the dimension by which the card should be sorted. At some point in the trial, the experimenter changes the sorting criterion, and the participant must deduce the new order.

word-stem completion task

Test in which participants are given a list of words to study. After a delay, memory for the words is tested in two ways, both of which involve the presentation of three-letter stems. In the cued-recall condition, participants are asked to recall the word from the study list that started with those same three letters. In the word-stem

completion condition, individuals are to report “the first word that comes to mind” that completes each stem.

References

Chapter 1

Abi-Dargham, A., Xu, X., Thompson, J. L., Gil, R., Kegeles, L. S., Urban, N., et al. (2012). Increased prefrontal cortical D₁ receptors in drug naive patients with schizophrenia: A PET study with [¹¹C]NNC112. *Journal of Psychopharmacology* (Oxford, England), **26**(6), 794–805.

Aboitiz, F., Scheibel, A. B., Fisher, R. S., and Zaidel, E. (1992). Fiber composition of the human corpus callosum. *Brain Research*, **598**(1–2), 143–153.

Apaydin, E. A., Maher, A. R., Shanman, R., Booth, M. S., Miles, J. N. V., Sorbero, M. E., and Hempel, S. (2016). A systematic review of St. John's wort for major depressive disorder. *Systematic Reviews*, **5**(1), 148.

Arnsten, A. F. T. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Sciences*, **2**, 436–447.

Bartus, R. T. (2000). On neurodegenerative diseases, models, and treatment strategies: Lessons learned and lessons forgotten a generation following the cholinergic hypothesis. *Experimental Neurology*, **163**, 495–529.

Beaubrun, G., and Gray, G. E. (2000). A review of herbal medicines for psychiatric disorders. *Psychiatric Services*, **51**, 1130–1134.

Bechara, A. (2004). The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. *Brain and Cognition*, **55**(1), 30–40.

Benishin, C. G., Lee, R., Wang, L. C. H., and Liu, H. J. (1991). Effects of ginsenoside Rb1 on central cholinergic metabolism. *Pharmacology*, **42**, 223–229.

Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., and Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics*, **12**, 81–84.

Berridge, C. W. (2008). Noradrenergic modulation of arousal. *Brain Research Reviews*, **58**(1), 1–17.

Berridge, K. C., and Kringelbach, M. L. (2015). Pleasure systems in the brain. *Neuron*, **86**(3), 646–664.

Biederman, J., Arnsten, A. F. T., Faraone, S. V., Doyle, A. E., Spencer, T. J., Wilens, T. E., Weiss, M. D., Safren, S. A., and Culpepper, L. (2006). New developments in the treatment of ADHD. *Journal of Clinical Psychiatry*, **67**, 148–159.

Breska, A., and Ivry, R. B. (2016). Taxonomies of timing: Where does the cerebellum fit in? *Current Opinion in Behavioral Sciences*, **8**, 282–288.

Cahill, L., Pham, C. A., and Setlow, B. (2000). Impaired memory consolidation in rats produced with beta-adrenergic blockade. *Neurobiology of Learning and Memory*, **74**, 259–266.

Chamberlain, S. R., Müller, U., Blackwell, A. D., Robbins, T. W., and Sahakian, B. J. (2006). Noradrenergic modulation of working memory and emotional memory in humans. *Psychopharmacology*, **188**, 397–407.

Coull, J. T., Middleton, H. C., Robbins, T. W., and Sahakian, B. J. (1995). Clonidine and diazepam have differential effects on tests of attention and learning. *Psychopharmacology*, **120**, 322–332.

Coull, J. T., Nobre, A. C., and Frith, C. D. (2001). The noradrenergic $\alpha 2$ agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cerebral Cortex*, **11**, 73–84.

DeKosky, S. T., Williamson, J. D., Fitzpatrick, A. L., Kronmal, R. A., Ives, D. G., Saxton, J. A., et al. (2008). Ginkgo biloba for prevention of dementia. *JAMA*, **300**, 2253–2262.

DeLuca, G. C., Yates, R. L., Beale, H., and Morrow, S. A. (2015). Cognitive impairment in multiple sclerosis: Clinical, radiologic and pathologic insights. *Brain Pathology* (Zurich, Switzerland), **25**(1), 79–98.

De Renzi, E. (2000). Prosopagnosia. In M. J. Farah and T. E. Feinberg (eds.), *Patient-based approaches to cognitive neuroscience* (pp. 85–95). Cambridge, MA: MIT Press.

Do Rego, J. C, Benkiki, N., Chosson, E., Kabouche, Z., Seguin, E., and Costentin, J. (2007). Antidepressant-like effect of hyperfoliatin, a polyisoprenylated phloroglucinol derivative from *Hypericum perforatum* (Clusiaceae) is associated with an inhibition of neuronal monoamines uptake. *European Journal of Pharmacology*, **569**, 197–203.

Durstewitz, D., and Seamans, J. K. (2008). The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. *Biological Psychiatry*, **64**(9), 739–749.

Farah, M. J., and Feinberg, T. E. (2000). Visual object agnosia. In M. J. Farah and T. E. Feinberg (eds.), *Patient-based approaches to cognitive neuroscience* (pp. 79–84). Cambridge, MA: MIT Press.

Farahani, M. S., Bahramsoltani, R., Farzaei, M. H., Abdollahi, M., and Rahimi, R. (2015). Plant-derived natural medicines for the management of depression: An overview of mechanisms of action. *Reviews in the Neurosciences*, **26**(3), 305–321.

Fowler, J. S., Wang, G. J., Volkow, N. D., Logan, J., Franceschi, D., Franceschi, M., MacGregor, R., Shea, C., Garza, V., Liu, N., and Ding, Y. S. (2000). Evidence that ginkgo biloba extract does not inhibit MAO A and B in living human brain. *Life Science*, **66**, 141–146.

Geromichalos, G. D., Lamari, F. N., Papandreou, M. A., Trafalis, D. T., Margarity, M., Papageorgiou, A., Sinakos, Z. (2012). Saffron as a source of novel acetylcholinesterase inhibitors: Molecular docking and in vitro enzymatic studies. *Journal of Agricultural*

and Food Chemistry, **60**(24), 6131–6138.

Gross, C. G., Rocha-Miranda, C. E., and Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. *Journal of Neurophysiology*, **35**, 96–111.

Hofer, S., and Frahm, J. (2006). Topography of the human corpus callosum revisited: Comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *NeuroImage*, **32**(3), 989–994.

Hurlemann, R., Hawellek, B., Matusch, A., Kolsch, H., Wollersen, H., Madea, B., Vogetley, K., Maier, W., and Dolan, R. J. (2005). Noradrenergic modulation of emotion-induced forgetting and remembering. *Journal of Neuroscience*, **25**, 6343–6349.

Kassel, J. (1997). Smoking and attention: A review and reformulation of the stimulus-filter hypothesis. *Clinical Psychology Review*, **17**, 451–478.

Kavanagh, S., van Baelen, B., and Schäuble, B. (2011). Long-term effects of galantamine on cognitive function in Alzheimer's disease: A large-scale international retrospective study. *Journal of Alzheimer's Disease*, **27**(3), 521–530.

Kim, D. H., Park, S. J., Kim, J. M., Jeon, S. J., Kim, D.-H., Cho, Y.-W., et al. (2011). Cognitive dysfunctions induced by a cholinergic blockade and A β 25–35 peptide are attenuated by salvianolic acid B. *Neuropharmacology*, **61**(8), 1432–1440.

Klinkenberg, I., and Blokland, A. (2010). The validity of scopolamine as a pharmacological model for cognitive impairment: A review of animal behavioral studies. *Neuroscience and Biobehavioral Reviews*, **34**(8), 1307–1350.

Kumar, A., Ghosal, S., and Bigl, V. (1997). Systematic administration of defined extracts from *Withania somnifera* (Indian Ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain. *Neurochemistry International*, **30**, 181–190.

Kumar, H., More, S. V., Han, S.-D., Choi, J.-Y., and Choi, D.-K. (2012). Promising therapeutics with natural bioactive compounds for improving learning and memory: A review of randomized trials. *Molecules*, **17**(9), 10503–10539.

LeBars, P. L., Katz, M. M., Berman, N., Itil, T. M., Freedman, A. M., and Schatzberg, A. F. (1997). A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb study group. *JAMA*, **278**, 1327–1332.

Mazza, M., Capuano, A., Bria, P., and Mazza, S. (2006). *Ginkgo biloba* and donepezil: A comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *European Journal of Neurology*, **13**, 981–985.

Miwa, H., Iijima, M., Tanaka, S., and Mizuno, Y. (2001). Generalized convulsions after consuming a large amount of ginkgo nuts. *Epilepsia*, **42**, 280–281.

Modabbernia, A., and Akhondzadeh, S. (2013). Saffron, passionflower, valerian and sage for mental health. *The Psychiatric Clinics of North America*, **36**(1), 85–91.

Möhler, H. (2008). GABAA receptors in central nervous system disease: Anxiety, epilepsy, and insomnia. *Journal of Receptors and Signal Transduction*, **26**, 731–740.

Moll, J., and de Oliveira-Souza, R. (2007). Moral judgments, emotions and the utilitarian brain. *Trends in Cognitive Science*, **11**(8), 319–321.

Montes, P., Ruiz-Sanchez, E., Rojas, C., and Rojas, P. (2015). *Ginkgo biloba* extract 761: A review of basic studies and potential clinical use in psychiatric disorders. *CNS and Neurological Disorders Drug Targets*, **14**(1), 132–149.

Mowry, E. M., Beheshtian, A., Waubant, E., Goodin, D. S., Cree, B. A., Qualley, P., Lincoln, R., George, M. F., Gomez, R., Hauser, S. L., Okuda, D. T., and Pelletier, D. (2009). Quality of life in multiple sclerosis is associated with lesion burden and brain

volume measures. *Neurology*, **72**, 1760–1765.

Munafò, M. R., Yalcin, B., Willis-Owen, S. A., and Flint, J. (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: Meta-analysis and new data. *Biological Psychiatry*, **63**(2), 197–206.

Nemoda, Z., Szekely, A., and Sasvari-Szekely, M. (2011). Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood. *Neuroscience and Biobehavioral Reviews*, **35**(8), 1665–1686.

Ng, Q. X., Venkatanarayanan, N., and Ho, C. Y. X. (2017). Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis. *Journal of Affective Disorders*, **210**, 211–221. <http://doi.org/10.1016/j.jad.2016.12.048>

Olsen, R. W., DeLorey, T. M., Gordey, M., and Kang, M. H. (1999). GABA receptor function and epilepsy. *Advances in Neurology*, **79**, 499–510.

Olvera-Cortés, M. E., Anguiano-Rodriguez, P., López-Vázquez, M. A., and Alfaro, J. M. C. (2008). Serotonin/dopamine interaction in learning. *Progress in Brain Research*, **172**, 567–602.

Perrett, D. I., Mistlin, A. J., and Chitty, A. J. (1987). Visual neurones responsive to faces. *Trends in Neurosciences*, **10**, 358–364.

Perry, E., and Howes, M.-J. R. (2011). Medicinal plants and dementia therapy: Herbal hopes for brain aging? *CNS Neuroscience and Therapeutics*, **17**(6), 683–698. <http://doi.org/10.1111/j.1755-5949.2010.00202.x>

Perry, N., Court, G., Bidet, N., and Court, J. (1996). European herbs with cholinergic activities: Potential in dementia therapy. *International Journal of Geriatric Psychiatry*, **11**, 1063–1069.

Poorthuis, R., Goriounova, N., Couey, J., and Mansvelder, H. (2009). Nicotinic actions

on neuronal networks for cognition: General principles and long-term consequences. *Biochemical Pharmacology*, **78**(7), 668–76. <http://doi.org/10.1016/j.bcp.2009.04.031>

Ramachandran, V. S., Rogers-Ramachandran, D., and Steward, M. (1992). Perceptual correlates of massive cortical reorganization. *Science*, **258**, 1159–1160.

Reist, C., Duffy, J. G., Fujimoto, K., and Cahill, L. (2001). Beta-adrenergic blockade and emotional memory in PTSD. *International Journal of Neuropsychopharmacology*, **4**, 377–383.

Riedel, W. M., Klaassen, T., Deutz, N. E. P., van Someren, A., and van Praag, H. M. (1999). Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. *Psychopharmacology*, **141**, 362–369.

Sarter, M., Hasselmo, M. E., Bruno, J. P., and Givens, B. (2005). Unraveling the attentional functions of cortical cholinergic inputs: Interactions between signal-driven and cognitive modulation of signal detection. *Brain Research Reviews*, **48**, 98–111.

Sawaguchi, T., and Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science*, **251**, 947–950.

Saxe, R. (2006). Uniquely human social cognition. *Current Opinion in Neurobiology*, **16**, 235–239.

Schmitt, J. A. J., Wingen, M., Ramaekers, J. G., Evers, E. A. T., and Riedel, W. J. (2006). Serotonin and human cognitive performance. *Current Pharmaceutical Design*, **12**, 2473–2486.

Simmonds, D. J., Hallquist, M. N., Asato, M., and Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, **92**, 356–368.

Solomon, P. R., Adams, F., Silver, A., Zimmer, J., and DeVeaux, R. (2002). Ginkgo for memory enhancement: A randomized controlled trial. *JAMA*, **288**, 835–840.

Spillane, J. A., White, P., Goodhart, W. J., Flack, R. H., Bowen, D. M., and Davison, A. N. (1977). Selective vulnerability of neurones in organic dementia. *Nature*, **266**, 558–559.

Stevens, M. C. (2016). The contributions of resting state and task-based functional connectivity studies to our understanding of adolescent brain network maturation. *Neuroscience and Biobehavioral Reviews*, **70**, 13–32.

Stoodley, C. J. (2012). The cerebellum and cognition: Evidence from functional imaging studies. *Cerebellum* (London, England), **11**(2), 352–365.

Tan, M.-S., Yu, J.-T., Tan, C.-C., Wang, H.-F., Meng, X.-F., Wang, C., et al. (2015). Efficacy and adverse effects of ginkgo biloba for cognitive impairment and dementia: A systematic review and meta-analysis. *Journal of Alzheimer's Disease: JAD*, **43**(2), 589–603.

Taylor, S. F., Stern, E. R., and Gehring, W. J. (2007). Neural systems for error monitoring: Recent findings and theoretical perspectives. *Neuroscientist*, **13**, 60–72.

Ungerleider, L. G., and Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, and R. J. W. Mansfield (eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

Vellas, B., Coley, N., Ousset, P.-J., Berrut, G., Dartigues, J.-F., Dubois, B., et al. (2012). Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. *The Lancet. Neurology*, **11**(10), 851–859.

von Gunten, A., Schlaefke, S., and Überla, K. (2016). Efficacy of Ginkgo biloba extract

EGb 761(®) in dementia with behavioural and psychological symptoms: A systematic review. *The World Journal of Biological Psychiatry*, **17**(8), 622–633.

Wake, G., Court, J., Pickering, A., Lewis, R., Wilkins, R., and Perry, E. (2000). CNS acetylcholine receptor activity in European medicinal plants traditionally used to improve failing memory. *Journal of Ethnopharmacology*, **69**, 105–114.

Warrington, E. K., and James, M. (1988). Visual apperceptive agnosia: A clinico-anatomical study of three cases. *Cortex*, **24**, 13–32.

Wettstein, A. (2000). Cholinesterase inhibitors and Ginkgo extracts – Are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. *Phytomedicine*, **6**, 393–401.

Zakzanis, K. K., Campbell, Z., and Jovanovski, D. (2007). The neuropsychology of ecstasy (MDMA) use: A quantitative review. *Human Psychopharmacology*, **22**, 427–435.

Zuchero, J. B., and Barres, B. A. (2015). Glia in mammalian development and disease. *Development (Cambridge, England)*, **142**(22), 3805–3809.

Chapter 2

Allison, T., McCarthy, G., Nobre, A., Puce, A., and Belger, A. (1994). Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. *Cerebral Cortex*, **5**, 544–554.

Annett, M. (1985). *Left, right, hand and brain: The right shift theory*. London: Lawrence Erlbaum Associates.

Annett, M. (1995). The right shift theory of a genetic balanced polymorphism for cerebral dominance and cognitive processing. *Current Psychology of Cognition*, **14**, 427–480.

Banich, M. T. (1998). The missing link: The role of interhemispheric interaction in attentional processing. *Brain and Cognition*, **36**(2), 128–157.

Banich, M. T. (2003). Interaction between the hemispheres and its implications for the processing capacity of the brain. In R. Davidson and K. Hugdahl (eds.), *Brain asymmetry* (2nd edn.) (pp. 261–302). Cambridge, MA: MIT Press.

Banich, M. T., and Belger, A. (1990). Interhemispheric interaction: How do the hemispheres divide and conquer a task? *Cortex*, **26**, 77–94.

Banich, M. T., and Brown, W. S. (2000). A life-span perspective on interaction between the cerebral hemispheres. *Developmental Neuropsychology*, **18**(1), 1–10.

Banich, M. T., Passarotti, A. M., and Janes, D. (2000). Interhemispheric interaction during childhood: I. Neurologically intact children. *Developmental Neuropsychology*, **18**(1), 33–51.

Beeman, M. J., and Chiarello, C. (1998a). Complementary right-and left-hemisphere language comprehension. *Current Directions in Psychological Science*, **7**(1), 2–8.

Beeman, M. J., and Chiarello, C. (eds.) (1998b). Right hemisphere language comprehension: Perspectives from cognitive neuroscience. Mahwah, NJ: Lawrence Erlbaum and Associates.

Belger, A., and Banich, M. T. (1992). Interhemispheric interaction affected by computational complexity. *Neuropsychologia*, **30**, 923–931.

Belger, A., and Banich, M. T. (1998). Costs and benefits of integrating information between the cerebral hemispheres: A computational perspective. *Neuropsychology*, **12**(3), 380–398.

Benton, A. L., Hannay, H. J., and Varney, N. R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology*, **25**, 907–910.

Borod, J. C., Carper, M., Naeser, M., and Goodglass, H. (1985). Left-handed and right-handed aphasics with left hemisphere lesions compared on nonverbal performance measures. *Cortex*, **21**, 81–90.

Bowers, D., Bauer, R. M., Coslett, H. B., and Heilman, K. M. (1985). Processing of faces by patients with unilateral hemispheric lesions. I. Dissociations between judgements of facial affect and facial identity. *Brain and Cognition*, **4**, 258–272.

Bryden, M. P. (1965). Tachistoscopic recognition, handedness, and cerebral dominance. *Neuropsychologia*, **3**, 1–8.

Cai, Q., van der Haegen, L., and Brysbaert, M. (2013). Complementary hemispheric specialization for language production and visuospatial attention. *Proceedings of the National Academy of Sciences USA*, **110**, E322–E330.

Caramazza, A., and Badecker, W. (1989). Patient classification in neuropsychological research. *Brain and Cognition*, **10**, 256–295.

Catani, M., and Ffytche, D. H. (2005). The rises and falls of disconnection syndromes.

Brain: A Journal of Neurology, **128**(Pt. 10), 2224–2239.

Chabris, C. F., and Kosslyn, S. M. (1998). How do the cerebral hemispheres contribute to encoding spatial relations? *Current Directions in Psychological Science*, **7**(1), 8–14.

Corballis, M. C. (2012). Lateralization of the human brain. *Progress in Brain Research*, **195**, 103–121.

Damasio, H. (1995). *Human Brain Anatomy in Computerized Images* (1st edn.). Oxford: Oxford University Press.

Damasio, H., and Damasio, A. R. (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.

Davis, S. W., Kragel, J. E., Madden, D. J., and Cabeza, R. (2012). The architecture of cross-hemispheric communication in the aging brain: Linking behavior to functional and structural connectivity. *Cerebral Cortex*, **22**(1), 232–242.

Dennis, N. A., and Cabeza, R. (2008). Neuroimaging of healthy cognitive aging. In F. I. M. Craik, T. A. Salthouse (eds.), *The handbook of aging and cognition* (pp. 1–54). Mahwah, NJ: Lawrence Erlbaum.

Desimone, R., Albright, T. D., Gross, C. G., and Bruce, C. (1984). Stimulus selective properties of inferior temporal neurons in the macaque. *Journal of Neuroscience*, **4**, 2051–2062.

Donchin, E., Ritter, W., and McCallum, W. C. (1978). Cognitive psychophysiology: The endogenous components of the ERP. In E. Callaway, P. Tueting, and S. H. Koslow (eds.), *Event-related brain potentials in man* (pp. 349–441). New York: Academic Press.

Dronkers, N. F., Plaisant, O., Iba-Zizen, M. T., and Cabanis, E. A. (2007). Paul Broca's historic cases: High resolution MR imaging of the brain of Leborgne and Lelong. *Brain*,

130, Figure 3, page 1436.

Ehrman, L., and Perelle, I. (1983). Laterality. *Mensa Research Journal*, **16**:3–32.

Erickson, K. M., and Cole, D. J. (2007). Anesthetic considerations for awake craniotomy for epilepsy. *Anesthesiology Clinics*, **25**(3), 535–555, figure 1, page 540.

Fodor, J. (1985). The modularity of mind. *Behavioral and Brain Sciences*, **8**, 1–42.

Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. (1991). Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, **65**(6), 1464–1483.

Galambos, R., and Sheatz, G. C. (1962). An electroencephalographic study of classical conditioning. *American Journal of Physiology*, **203**, 173–184.

Gatley, J., Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Ding, Y-S., and Gerasimov, M. (2005). PET imaging in clinical drug abuse research. *Current Pharmaceutical Design*, **11**, 3203–3219.

Gazzaniga, M. S. (1970). *The bisected brain*. New York: Appleton-Century-Crofts.

Gazzaniga, M. S. (1983a). Right hemisphere language following brain bisection: A 20-year perspective. *American Psychologist*, **38**, 525–537.

Gazzaniga, M. S. (1983b). Reply to Levy and Zaidel. *American Psychologist*, **38**, 547–549.

Gazzaniga, M. S. (2000). Cerebral specialization and inter-hemispheric communication: Does the corpus callosum enable the human condition? *Brain*, **123**, 1293–1326.

Gazzaniga, M. S. (2005). Forty-five years of split-brain research and still going strong. *Nature Reviews Neuroscience*, **6**, 653–659.

Gazzaniga, M. S., Bogen, J. E., and Sperry, R. W. (1962). Some functional effects of sectioning the cerebral commissures in man. *Proceedings of the National Academy of Sciences of the United States of America*, **48**, 1765–1769.

Georgopoulos, A. P., Schwartz, A. B., and Kettner, R. E. (1986). Neuronal population coding of movement direction. *Science*, **233**, 1416–1419.

Geschwind, N. (1965a). Disconnexion syndromes in animals and man. I. *Brain*, **88**, 237–294.

Geschwind, N. (1965b). Disconnexion syndromes in animals and man. II. *Brain*, **88**, 585–644.

Geschwind, N., and Levitsky, W. (1968). Human brain left–right asymmetries in temporal speech region. *Science*, **161**, 186–187.

Gibson, C., and Bryden, M. P. (1983). Dichaptic recognition of shapes and letters in children. *Canadian Journal of Psychology*, **37**, 132–143.

Gordon, H. W. (1980). Degree of ear asymmetries for perception of dichotic chords and for illusory chord localization in musicians of different levels of competence. *Journal of Experimental Psychology: Human Perception and Performance*, **6**, 516–527.

Gorvine, B., Rosengren, K., Stein, L., and Biolsi, K. (2017). *Research methods: From theory to practice*. Oxford: Oxford University Press.

Greenberg, J. H., Reivich, M., Alavi, A., Hand, P., Rosenquist, A., Rintelmann, W., et al. (1981). Metabolic mapping of functional activity in human subjects with the [18 F]fluorodeoxyglucose technique. *Science*, **212**(4495), 678–680.

Gross, C. G., Rocha-Miranda, C. E., and Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. *Journal of Neurophysiology*, **35**, 96–111.

Harris, L. J. (1999). Early theory and research on hemispheric specialization. *Schizophrenia Bulletin*, **25**(1), 11–39.

Hécaen, H., De Agostini, M., Monzon-Montes, A. (1981). Cerebral organization in left-handers. *Brain Lang*, **12**, 261–284.

Höller-Wallscheid, M. S., Thier, P., Pomper, J. K., and Lindner, A. (2017). Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age. *Proceedings of the National Academy of Sciences*, **114**(5), E830–E839.

Ivry, R. B., and Robertson, L. C. (1998). *The two sides of perception*. Cambridge, MA: MIT Press.

Kimura, D. (1967). Functional asymmetry of the brain in dichotic listening. *Cortex*, **3**, 164–178.

Kinsbourne, M. (1975). The mechanisms of hemispheric control of the lateral gradient of attention. In P. M. A. Rabbitt and S. Dornic (eds.), *Attention and performance*. New York: Academic Press.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, P. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H.-M., Brady, T. J., and Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences*, **89**, 5675–5679.

Lashley, K. S. (1929). *Brain mechanisms and intelligence*. Chicago: University of Chicago Press.

Levine, S. C., and Banich, M. T. (1982). Lateral asymmetries in the naming of words and corresponding line drawings. *Brain and Language*, **17**, 34–45.

Levine, S. C., Banich, M. T., and Koch-Weser, M. (1988). Face recognition: A general or specific right hemisphere capacity? *Brain and Cognition*, **8**, 303–325.

Levy, J. (1983). Language, cognition, and the right hemisphere: A response to Gazzaniga. *American Psychologist*, **38**, 538–541.

Levy, J., and Trevarthen, C. W. (1977). Perceptual, semantic and phonetic aspects of elementary language processes in split-brain patients. *Brain*, **100**, 105–118.

Levy, J., Trevarthen, C. W., and Sperry, R. W. (1972). Perception of bilateral chimeric figures following “hemispheric deconnexion.” *Brain*, **95**, 61–78.

McManus, C. (2002). Right hand, left hand: The origins of asymmetry in brains, bodies, atoms and cultures. Cambridge, MA: Harvard University Press.

Medland, S. E., Duffy, D. L., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., et al. (2009). Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families. *Neuropsychologia*, **47**(2), 330–337.

<http://doi.org/10.1016/j.neuropsychologia.2008.09.005>

Milner, B. (1978). Clues to the cerebral organization of memory. In P. Buser and A. Rougeul-Buser (eds.), *Cerebral correlates of conscious experience*. Amsterdam: Elsevier.

Milner, B., Taylor, L., and Sperry, R. W. (1968). Lateralized suppression of dichotically presented digits after commissural section in man. *Science*, **161**, 184–185.

Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society of London, Series B*, **298**, 85–95.

Moran, J., and Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. *Science*, **229**, 782–784.

Naeser, M. A., and Borod, J. C. (1986). Aphasia in left-handers: Lesion site, lesion side and hemispheric asymmetries on CT. *Neurology*, **36**, 471–488.

Novelly, R. A. (1992). The debt of neuropsychology to the epilepsies. *American Psychologist*, **47**, 1126–1129.

O'Boyle, M. W., van Wyhe-Lawler, F., and Miller, D. A. (1987). Recognition of letters traced in the right and left palms: Evidence for a process-oriented tactile asymmetry. *Brain and Cognition*, **6**, 474–494.

Ojemann, G. A. (1983). Brain organization for language from the perspective of electrical stimulation mapping. *Behavioral and Brain Sciences*, **6**, 189–230.

Papadatou-Pastou, M., and Tomprou, D.-M. (2015). Intelligence and handedness: Meta-analyses of studies on intellectually disabled, typically developing, and gifted individuals. *Neuroscience and Biobehavioral Reviews*, **56**, 151–165.

Penfield, W., and Jasper, H. (1954) *Epilepsy and the functional anatomy of the human brain*. Boston: Little, Brown.

Penfield, W., and Rasmussen, T. (1950). *The cerebral cortex of man: A clinical study of localization of function*. New York: Macmillan.

Perelle, I. B., and Ehrman, L. (1994). An international study of human handedness: The data. *Behavior Genetics*, **24**, 217–227.

Petersen, S. E., Fox, P. T., Posner, M. I., Ma, M., and Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, **6157**, 585–589.

Pigott, S., and Milner, B. (1993). Memory for different aspects of complex visual scenes after unilateral temporal or frontal-lobe resection. *Neuropsychologia*, **31**, 1–15.

Posner, M. I., and Raichle, M. E. (1994). *Images of mind*. New York: Freeman.

Quiian Quiroga, R., Reddy, L., Kreiman, G., Koch, C., and Fried, I. (2005). Invariant visual representation by single neurons in the human brain. *Nature*, **435**, 1102–1107.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A.-M. K., Pardo, J. V., Fox, P. T., Petersen, S. E. (1994). Practice-related changes in human brain functional anatomy during non-motor learning. *Cerebral Cortex*, **4**: 8–26.

Rasmussen, T., and Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences*, **299**, 355–369.

Reuter-Lorenz, P. A., Stanczak, L. M., and Miller, A. C. (1999). Neural recruitment and cognitive aging: Two hemispheres are better than one, especially as you age. *Psychological Science*, **10**(6), 494–500.

Robertson, L. C., and Ivry, R. (2000). Hemispheric asymmetries: Attention to visual and auditory primitives. *Current Directions in Psychological Science*, **9**, 59–63.

Robertson, L. C., and Lamb, M. R. (1991). Neuropsychological contributions to part/whole organization. *Cognitive Psychology*, **23**, 299–332.

Rorden, C., and Karnath, H. O. (2004). Using human brain lesions to infer function: A relic from a past era in the fMRI age? *Nature Reviews Neuroscience*, **5**, 813–819.

Ross, E. D. (1981). The aprosodias: Functional-anatomic organization of the affective components of language in the right hemisphere. *Archives of Neurology*, **38**, 561–569.

Sandman, C. A., O'Halloran, J. P., and Isenhardt, R. (1984). Is there an evoked vascular response? *Science*, **224**, 1355–1367.

Sandu, A.-L., Izard, E., Specht, K., Beneventi, H., Lundervold, A., and Ystad, M.

(2014). Post-adolescent developmental changes in cortical complexity. *Behavioral and Brain Functions: BBF*, **10**(1), 44, figure 2, page 4. <http://doi.org/10.1186/1744-9081-10-44>.

Saron, C. D., and Davidson, R. J. (1989). Visual evoked potential measures of interhemispheric transfer time in humans. *Behavioral Neuroscience*, **103**, 1115–1138.

Sergent, J. (1990). Furtive incursions into bicameral minds. *Brain*, **113**, 537–568.

Shallice, T. (1988). *From neuropsychology to mental structure*. Cambridge: Cambridge University Press.

Somers, M., Ophoff, R. A., Aukes, M. F., Cantor, R. M., Boks, M. P., Dauwan, M., et al. (2015). Linkage analysis in a Dutch population isolate shows no major gene for left-handedness or atypical language lateralization. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **35**(23), 8730–8736. <http://doi.org/10.1523/JNEUROSCI.3287-14.2015>

Sperry, R. W. (1961). Cerebral organization and behavior: The split brain behaves in many respects like two separate brains, providing new research possibilities. *Science*, **133**(3466), 1749–1757.

Sperry, R. W., Zaidel, E., and Zaidel, D. (1979). Self recognition and social awareness in the disconnected minor hemisphere. *Neuropsychologia*, **17**, 153–166.

Steinmetz, H., Rademacher, J., Huang, Y., Hefter, H., Zilles, K., Thron, A., and Freund, H.-J. (1989). Cerebral asymmetry: MR planimetry of the human planum temporale. *Journal of Computer Assisted Tomography*, **13**, 996–1005.

Stelzer, J., Lohmann, G., Mueller, K., Buschmann, T., and Turner, R. (2014). Deficient approaches to human neuroimaging. *Frontiers in Human Neuroscience*, **8**, 462. <http://doi.org/10.3389/fnhum.2014.00462>

Stone, J., Davis, J., Leucht, S., and Pilowsky, L. (2009). Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs: An original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. *Schizophrenia Bulletin*, **35**(4), 789–797.

Stone, J. L., and Hughes, J. R. (2013). Early history of electroencephalography and establishment of the American Clinical Neurophysiology Society. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society*, **30**(1), 28–44.

Studdert-Kennedy, M., and Shankweiler, D. (1970). Hemispheric specialization for speech perception. *Journal of the Acoustical Society of America*, **48**, 579–594.

Sutton, S., Braren, M., Zubin, J., and John, E. R. (1965). Evoked potential correlates of stimulus uncertainty. *Science*, **150**, 1187–1188.

Teuber, H. L. (1955). Physiological psychology. *Annual Review of Psychology*, **6**, 267–296.

Toga, A. W., and Thompson, P. M. (2003). Mapping brain asymmetry. *Nature Reviews Neuroscience*, **4**(1), 37–48.

Tzourio, N., Nkanga-Ngila, B., Mazoyer, B. (1998). Left planum temporale surface correlates with functional dominance during story listening. *Neuroreport*, **9**, 829–833.

Tzourio-Mazoyer, N., Petit, L., Razafimandimby, A., Crivello, F., Zago, L., Jobard, G., et al. (2010). Left hemisphere lateralization for language in right-handers is controlled in part by familial sinistrality, manual preference strength, and head size. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **30**(40), 13314–13318. <http://doi.org/10.1523/JNEUROSCI.2593-10.2010>

Tzourio-Mazoyer, N., Simon, G., Crivello, F., Jobard, G., Zago, L., Perchey, G., et al.

(2010). Effect of familial sinistrality on planum temporale surface and brain tissue asymmetries. *Cerebral Cortex*, **20**(6), 1476–1485.

<http://doi.org/10.1093/cercor/bhp209>

Vallortigara, G., and Rogers, L. J. (2005). Survival with an asymmetrical brain: Advantages and disadvantages of cerebral lateralization. *Behavioral and Brain Sciences*, **28**, 575–633.

Wada, J., and Rasmussen, T. (1960). Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: Experimental and clinical observations. *Journal of Neurosurgery*, **17**(2).

Warrington, E. K., and Taylor, A. M. (1973). The contribution of the right parietal lobe to object recognition. *Cortex*, **9**, 152–164.

Watila, M. M., and Balarabe, S. A. (2015). Factors predicting post-stroke aphasia recovery. *Journal of the Neurological Sciences*, **352**(1–2), 12–18.

Wehrli, F. W. (2004). On the 2003 Nobel Prize in medicine or physiology awarded to Paul C. Lauterbur and Sir Peter Mansfield. *Magnetic Resonance in Medicine*, **51**, 1–3.

Willems, R. M., Peelen, M. V., and Hagoort, P. (2010). Cerebral lateralization of face-selective and body-selective visual areas depends on handedness. *Cerebral Cortex*, **20**, 1719–1725.

Willems, R. M., van der Haegen, L., Fisher, S. E., and Francks, C. (2014). On the other hand: including left-handers in cognitive neuroscience and neurogenetics. *Nature Reviews Neuroscience*, **15**(3), 193–201.

Witelson, S. F. (1974). Hemisphere specialization for linguistic and nonlinguistic tactual perception using a dichotomous stimulation technique. *Cortex*, **10**, 3–17.

Wong, D. F., Wagner, H. N., Tune, L. E., Dannals, R. F., et al. (1986). Positron emission

tomography revealed elevated D2 receptors in drug-naïve schizophrenics. *Science*, **234**, 1558–1563.

Yin, R. K. (1970). Face recognition by brain-injured patients: A dissociable ability? *Neuropsychologia*, **8**, 395–402.

Zaidel, E. (1978). Auditory language comprehension in the right hemisphere following cerebral commissurotomy and hemispherectomy: A comparison with child language and aphasia. In A. Caramazza and E. B. Zurif (eds.), *Language acquisition and language breakdown: Parallels and divergencies* (pp. 229–275). Baltimore, MD: Johns Hopkins University Press.

Zaidel, E. (1983a). A response to Gazzaniga: Language in the right hemisphere, convergent perspectives. *American Psychologist*, **38**, 542–546.

Zaidel, E. (1983b). Disconnection syndrome as a model for laterality effects in the normal brain. In J. B. Hellige (ed.), *Cerebral hemisphere asymmetry: Method, theory and application* (pp. 95–151). New York: Praeger.

Zaidel, E. (1990). The saga of right-hemisphere reading. In C. Trevarthen (ed.), *Brain circuits and functions of the mind: Essays in honor of Roger W. Sperry* (pp. 304–319). Cambridge: Cambridge University Press.

Zurif, E. B., Gardner, J., and Brownell, H. H. (1989). The case against the case against group studies. *Brain and Cognition*, **10**, 237–255.

Chapter 3

Anderson, B., Mishory, A., Nahas, Z., Borckardt, J. J., Yamanaka, K., Rastogi, K., and George, M. S. (2006). Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *Journal of ECT*, **22**, 49–53.

Andrew, R. D., and MacVicar, B. A. (1994). Imaging cell volume changes and neuronal excitation in the hippocampal slice. *Neuroscience*, **62**, 371–383.

Andrews-Hanna, J. R., Mackiewicz Seghete, K. L., Claus, E. D., Burgess, G. C., Ruzic, L., and Banich, M. T. (2011). Cognitive control in adolescence: Neural underpinnings and relation to self-report behaviors. *PLoS ONE*, **6**(6), e21598.

<http://doi.org/10.1371/journal.pone.0021598>

Aslin, R. N., Shukla, M., and Emberson, L. L. (2015). Hemodynamic correlates of cognition in human infants. *Annual Review of Psychology*, **66**, 349–379.

Baillet, S. (2017). Magnetoencephalography for brain electrophysiology and imaging. *Nature Neuroscience*, **20**(3), 327–339.

Bandettini, P. (2007). Functional MRI today. *International Journal of Psychophysiology*, **63**, 138–145.

Batterink, L. J., Creery, J. D., and Paller, K. A. (2016). Phase of spontaneous slow oscillations during sleep influences memory-related processing of auditory cues. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **36**(4), 1401–1409.

Bersani, F. S., Minichino, A., Enticott, P. G., Mazzarini, L., Khan, N., Antonacci, G., et al. (2013). Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: A comprehensive review. *European Psychiatry: The Journal of the Association of European Psychiatrists*, **28**(1), 30–39.

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., et al. (2016). Safety of transcranial direct current stimulation: Evidence based update 2016. *Brain Stimulation*, **9**(5), 641–661. <http://doi.org/10.1016/j.brs.2016.06.004>

Birba, A., Ibanez, A., Sedeño, L., Ferrari, J., García, A. M., and Zimerman, M. (2017). Non-invasive brain stimulation: A new strategy in mild cognitive impairment? *Frontiers in Aging Neuroscience*, **9**, 16.

Biswal, B., Yetkin, F. Z., Haughton, V. M., and Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, **34**(4), 537–541.

Chumachenko, S. Y., Sakai, J. T., Dalwani, M. S., Mikulich-Gilbertson, S. K., Dunn, R., Tanabe, J., et al. (2015). Brain cortical thickness in male adolescents with serious substance use and conduct problems. *The American Journal of Drug and Alcohol Abuse*, **41**(5), 414–424. <http://doi.org/10.3109/00952990.2015.1058389>

Ciccarelli, O., Catani, M., Johansen-Berg, H., Clark, C., and Thompson, A. (2008). Diffusion-based tractography in neurological disorders: Concepts, applications and future developments. *Lancet Neurology*, **7**, 715–727.

Ciurleo, R., Bonanno, L., Di Lorenzo, G., Bramanti, P., and Marino, S. (2015). Metabolic changes in de novo Parkinson's disease after dopaminergic therapy: A proton magnetic resonance spectroscopy study. *Neuroscience Letters*, **599**, 55–60.

Coffman, B. A., Clark, V. P., and Parasuraman, R. (2014). Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*, **85**(Pt. 3), 895–908.

Cohen, J. D., Daw, N., Engelhardt, B., Hasson, U., Li, K., Niv, Y., et al. (2017). Computational approaches to fMRI analysis. *Nature Neuroscience*, **20**(3), 304–313.

Cohen, L. G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Damrosia, J., Honda, M., Sadato, N., Gerloff, C., Catalan, M. D., and Halett, M. (1997). Functional relevance of cross-modal plasticity in blind humans. *Nature*, **389**, 180–183.

Corbetta, M., Miezin, F. M., Shulman, G. L., and Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience*, **13**, 1202–1226.

Crawford, J. R. (1992). Current and premorbid intelligence measures in neuropsychological assessment. In J. R. Crawford, D. M. Parker, and W. W. McKinlay (eds.), *A handbook of neuropsychological assessment*. Hillsdale, NJ: Erlbaum.

de Aguiar, V., Paolazzi, C. L., and Miceli, G. (2014). tDCS in post-stroke aphasia: The role of stimulation parameters, behavioral treatment and patient characteristics. *Cortex*, **63**, 296–316.

de la Vega, A., Brown, M. S., Snyder, H. R., Singel, D., Munakata, Y., and Banich, M. T. (2014). Individual differences in the balance of gaba to glutamate in pFC predict the ability to select among competing options. *Journal of Cognitive Neuroscience*, **26**(11), 2490–2502. http://doi.org/10.1162/jocn_a_00655

Depue, B. E., Curran, T., and Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*, **317**(5835), 215–219. <http://doi.org/10.1126/science.1139560>

Depue, B. E., Ketz, N., Mollison, M. V., Nyhus, E., Banich, M. T., and Curran, T. (2013). ERPs and neural oscillations during volitional suppression of memory retrieval. *Journal of Cognitive Neuroscience*, **25**(10), 1624–1633.

Depue, B. E., Orr, J. M., Smolker, H. R., Naaz, F., and Banich, M. T. (2015). The organization of right prefrontal networks reveals common mechanisms of inhibitory regulation across cognitive, emotional, and motor processes. *Cerebral Cortex*, **26**(4), 1634–1646. <http://doi.org/10.1093/cercor/bhu324>

Donchin, E., and Coles, M. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences*, **11**, 406–417.

Ende, G. (2015). Proton magnetic resonance spectroscopy: Relevance of glutamate and gaba to neuropsychology. *Neuropsychology Review*, **25**(3), 315–325.
<http://doi.org/10.1007/s11065-015-9295-8>

Fabiani, M., Gratton, G., and Federmeier, K. (2007). Event-related brain potentials: Methods, theory and applications. In J. T. Cacioppo, L. G. Tassinary, and G. G. Berntson (eds.), *Handbook of psychophysiology* (3rd edn.) (pp. 85–119). Cambridge: Cambridge University Press.

Fauth, C., Meyer, B. U., Prosiegel, M., Zihl, J., and Conrad, B. E. (1992). Seizure induction and magnetic stimulation after stroke. *Lancet*, **339**, 362.

Ferreira, L. K., and Busatto, G. F. (2013). Resting-state functional connectivity in normal brain aging. *Neuroscience and Biobehavioral Reviews*, **37**(3), 384–400.

Forkel, S. J., Thiebaut de Schotten, M., Kawadler, J. M., Dell'Acqua, F., Danek, A., and Catani, M. (2014). The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. *Cortex*, **56**, 73–84, figure 2, page 79.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, **102**(27), 9673–9678.

Fox, P. T., Raichle, M. E., Mintun, M. A., and Dence, C. (1988). Nonoxidative glucose consumption during focal physiologic neural activity. *Science*, **241**, 462–464.

Gatley, J., Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Ding, Y.-S., and Gerasimov, M. (2005). PET imaging in clinical drug abuse research. *Current*

Pharmaceutical Design, **11**, 3203–3219.

Gershon, R. C., Wagster, M. V., Hendrie, H. C., Fox, N. A., Cook, K. F., and Nowinski, C. J. (2013). NIH toolbox for assessment of neurological and behavioral function. *Neurology*, **80**(11 Suppl. 3), S2–6.

Golden, C. J. (1981). A standardized version of Luria's neuropsychological tests. In S. Filskov and T. J. Boll (eds.), *Handbook of clinical neuropsychology*. New York: Wiley Interscience.

Golden, C. J., Purisch, A. D., and Hammeke, T. (1991). *Luria Nebraska Neuropsychological Battery: Forms I and II*. Los Angeles: Western Psychological Services.

Gratton, G., and Fabiani, M. (2010). Fast optical imaging of human brain function. *Frontiers in Human Neuroscience*, **4**, 52.

Grayson, D. S., and Fair, D. A. (2017). Development of large-scale functional networks from birth to adulthood: A guide to neuroimaging literature. *NeuroImage*, e-publication in advance of print.

Hajcak, G., MacNamara, A., and Olvet, D. M. (2010). Event-related potentials, emotion, and emotion regulation: An integrative review. *Developmental Neuropsychology*, **35**(2), 129–155.

Hampson, M., and Hoffman, R. E. (2010). Transcranial magnetic stimulation and connectivity mapping: Tools for studying the neural bases of brain disorders. *Frontiers in Systems Neuroscience*, **4**. <http://doi.org/10.3389/fnsys.2010.00040>

Hanslmayr, S., Gross, J., Klimesch, W., and Shapiro, K. L. (2011). The role of alpha oscillations in temporal attention. *Brain Research Reviews*, **67**(1–2), 331–343, Figure 1, page 333.

Haxby, J. V. (2012). Multivariate pattern analysis of fMRI: The early beginnings. *NeuroImage*, **62**(2), 852–855.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., and Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, **293**(5539), 2425–2430.

Heinen, K., Feredoes, E., Ruff, C. C., and Driver, J. (2017). Functional connectivity between prefrontal and parietal cortex drives visuo-spatial attention shifts. *Neuropsychologia*, **99**, 81–91.

Huddleston, W. E., and DeYoe, E. A. (2008). The representation of spatial attention in human parietal cortex dynamically modulated with performance. *Cerebral Cortex*, **18**, 1272–1280.

Ibanez, A., Melloni, M., Huepe, D., Helgiu, E., Rivera-Rei, A., Canales-Johnson, A., et al. (2012). What event-related potentials (ERPs) bring to social neuroscience? *Social Neuroscience*, **7**(6), 632–649.

Janicak, P. G., O'Reardon, J. P., Sampson, S. M., Husain, M. M., Lisanby, S. H., Rado, J. T., Heart, K. L., and Demitrack, M. A. (2008). Transcranial magnetic stimulation in the treatment of major depressive disorder: A comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *Journal of Clinical Psychiatry*, **69**, 222–232.

Jwa, A. (2015). Early adopters of the magical thinking cap: A study on do-it-yourself (DIY) transcranial direct current stimulation (tDCS) user community. *Journal of Law and the Biosciences*, **2**(2), 292–335.

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., and Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, **72**(6), 603–611.

Kosslyn, S. M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J. P., Thompson, W. L., Ganis, G., Sukel, K. E., and Alpert, N. M. (1999). The role of Area 17 in visual imagery: Convergent evidence from PET and rTMS. *Science*, **284**(5411), 167–170.

Kosslyn, S. M., Thompson, W. L., Kim, I. J., and Alpert, N. M. (1995). Topographical representations of mental images in primary visual cortex. *Nature*, **378**(6556), 496–498.

Kramer, A. F., Wickens, C. D., and Donchin, E. (1985). Processing of stimulus properties: Evidence for dual-task integrity. *Journal of Experimental Psychology: Human Perception and Performance*, **11**, 393–408.

Kutas, M., and Federmeier, K. D. (2011). Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology*, **62**, 621–647.

Kutas, M., and Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science*, **207**, 203–205.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, P. N., Hoppel, B. E., Cohen, M. S., Turner, R., Cheng, H.-M., Brady, T. J., and Rosen, B. R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences*, **89**, 5675–5679.

Lang, S., Duncan, N., and Northoff, G. (2014). Resting-state functional magnetic resonance imaging: Review of neurosurgical applications. *Neurosurgery*, **74**(5), 453–464; discussion 464–465.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., et al. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology: Official Journal*

of the International Federation of Clinical Neurophysiology, **125**(11), 2150–2206.

Lezak, M. D., Howieson, D. B., Bigler, E.D., and Tranel, D. (2012).
Neuropsychological assessment (5th edn.). Oxford: Oxford University Press.

Luck, S. J. (2014). ERP localization. In S. J. Luck, An introduction to the Event-related Potential Technique (2nd edn.). Cambridge, MA: MIT Press.

Luck, S. J., and Kappenman, E. S. (2012). ERP components. In E. S. Kappenman and S. J. Luck (eds.), The Oxford handbook of event-related potential components (pp. 1–57). New York: Oxford University Press.

Lynch, J. C., Mountcastle, V. B., Talbot, W. H., and Yin, T. C. (1977). Parietal lobe mechanisms for directed visual attention. *Journal of Neurophysiology*, **40**, 362–389.

Mangun, G. R., and Hillyard, S. A. (1990). Electrophysiological studies of visual selective attention in humans. In A. R. Scheibel and A. F. Wechsler (eds.), *Neurobiology of higher cognitive function* (pp. 271–295). New York: Guilford Press.

Martin, W. R. W. (2007). MR spectroscopy in neurodegenerative disease. *Molecular Imaging and Biology: MIB: The Official Publication of the Academy of Molecular Imaging*, **9**(4), 196–203.

Matthews, P. M., Honey, G. D., and Bullmore, E. T. (2006). Applications of fMRI in translational medicine and clinical practice. *Nature Reviews Neuroscience*, **7**, 732–744.

Modi, S., Rana, P., Kaur, P., Rani, N., and Khushu, S. (2014). Glutamate level in anterior cingulate predicts anxiety in healthy humans: A magnetic resonance spectroscopy study. *Psychiatry Research*, **224**(1), 34–41.

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., and Priori, A. (2013). Transcranial direct current stimulation (tDCS) and language. *Journal*

of Neurology, Neurosurgery, and Psychiatry, **84**(8), 832–842.

<http://doi.org/10.1136/jnnp-2012-302825>

Mori, S., and Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron*, **51**(5), 527–539.

<http://doi.org/10.1016/j.neuron.2006.08.012>

Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., and Husain, M. (2003). The anatomy of visual neglect. *Brain*, **126**, 1986–1997.

Näätänen, R., Gaillard, A. W. K., and Mantysalo, S. (1978). The N1 effect of selective attention reinterpreted. *Acta Psychologica (Amsterdam)*, **42**, 313–329.

Näätänen, R., and Kreegipuu, K. (2012). The Mismatch Negativity (MMN). In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potentials* (pp. 1–33). New York: Oxford.

<http://doi.org/10.1093/oxfordhb/9780195374148.013.0081>

Nelson, H. E. (1982). *National Adult Reading Test: Test manual*. Windsor, UK: NFER-Nelson.

O'Reilly, R. C., Munakata, Y., Frank, M. J., Hazy, T. E., and Contributors. (2012). *Computational Cognitive Neuroscience*. Wiki Book (1st edn.). URL:

<http://ccnbook.colorado.edu>

Orr, J. M., Paschall, C. J., and Banich, M. T. (2016). Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. *NeuroImage, Clinical*, **12**, 47–56.

Palta, P., Snitz, B., and Carlson, M. C. (2016). Neuropsychologic assessment. *Handbook of Clinical Neurology*, **138**, 107–119.

Palva, J. M., Monto, S., Kulashekhar, S., and Palva, S. (2010). Neuronal synchrony

reveals working memory networks and predicts individual memory capacity. *Proceedings of the National Academy of Sciences*, **107**(16), 7580–7585.

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., et al. (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex*, **19**(11), 2728–2735.

Paus, T., and Barrett, J. (2004). Transcranial magnetic stimulation (TMS) of the human frontal cortex: Implications for repetitive TMS treatment of depression. *Journal of Psychiatry and Neuroscience*, **29**, 268–279.

Paus, T., Castro-Alamancos, M. A., and Petrides, M. (2001). Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *European Journal of Neuroscience*, **14**, 1405–1411.

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., and Wirecki, T. S. (2016). The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. *Brain Stimulation*, **9**(3), 336–346.

Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., and Carpenter, L. L. (2017). Low-intensity transcranial current stimulation in psychiatry. *The American Journal of Psychiatry*. <http://doi.org/10.1176/appi.ajp.2017.16090996> (in press).

Polich, J. (2012). Neuropsychology of P300. In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potentials* (pp. 1–58). New York: Oxford University Press.

Pond❖❖, P. H., de Sena, E. P., Camprodon, J. A., de Araújo, A. N., Neto, M. F., DiBiasi, M., et al. (2017). Use of transcranial direct current stimulation for the treatment of auditory hallucinations of schizophrenia – a systematic review.

Neuropsychiatric Disease and Treatment, **13**, 347–355.

<http://doi.org/10.2147/NDT.S122016>

Potts, G. F., Liotti, M., Tucker, D. M., and Posner, M. I. (1996). Frontal and inferior temporal cortical activity in visual target detection: Evidence from high spatially sampled event-related potentials. *Brain Topography*, **9**(1), 3–14.

Pratt, H. (2012). Sensory ERP components. In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potentials* (pp. 1–58). New York: Oxford University Press.

Reineberg, A. E., Andrews-Hanna, J. R., Depue, B. E., Friedman, N. P., and Banich, M. T. (2015). Resting-state networks predict individual differences in common and specific aspects of executive function. *NeuroImage*, **104**, 69–78.

Reitan, R. M., and Wolfson, D. (1993). *The Halstead–Reitan neuropsychological test battery. Theory and clinical interpretation* (2nd edn.). Tucson, AZ: Neuropsychology Press.

Rigotti, D. J., Gonen, O., Grossman, R. I., Babb, J. S., Falini, A., Benedetti, B., and Filippi, M. (2011). Global N-acetylaspartate declines even in benign multiple sclerosis. *American Journal of Neuroradiology*, **32**(1), 204–209.

Roux, F., and Uhlhaas, P. J. (2014). Working memory and neural oscillations: α - γ versus θ - γ codes for distinct WM information? *Trends in Cognitive Sciences*, **18**(1), 16–25.

Rubinov, M., and Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, **52**(3), 1059–1069.

Russo, C., Souza Carneiro, M. I., Bolognini, N., and Fregni, F. (2017). Safety review of transcranial direct current stimulation in stroke. *Neuromodulation: Journal of the International Neuromodulation Society*, **20**(3), 215–222.

Saalmann, Y. B., Pigarev, I. N., and Vidyasagar, T. R. (2007). Neural mechanisms of visual attention: How top-down feedback highlights relevant locations. *Science*, **316**, 1612–1615.

Sandman, C. A., O'Halloran, J. P., and Isenhardt, R. (1984). Is there an evoked vascular response? *Science*, **224**, 1355–1367.

Scherg, M. (1992). Functional imaging and localization of electromagnetic brain activity. *Brain Topography*, **5**, 103–111.

Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, **275**(5306), 1593–1599.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., and Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology*, **37**, 257–261.

Schutter, D. J. (2009). Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham- controlled designs: A meta-analysis. *Psychological Medicine*, **39**, 65–75.

Sheffield, J. M., and Barch, D. M. (2016). Cognition and resting-state functional connectivity in schizophrenia. *Neuroscience and Biobehavioral Reviews*, **61**, 108–120.

Siebner, H. R., Hartwigsen, G., Kassuba, T., and Rothwell, J. C. (2009). How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex*, **45**(9), 1035–1042.

<http://doi.org/10.1016/j.cortex.2009.02.007>

Sigal, T., Shmuel, M., Mark, D., Gil, H., and Anat, A. (2012). Diffusion tensor imaging of corpus callosum integrity in multiple sclerosis: Correlation with disease variables. *Journal of Neuroimaging*, **22**(1), 33–37.

Silton, R. L., Heller, W., Towers, D. N., Engels, A. S., Spielberg, J. M., Edgar, J. C., et al. (2010). The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down attentional control. *NeuroImage*, **50**(3), 1292–1302.

Simmonds, D. J., Hallquist, M. N., Asato, M., and Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, **92**, 356–368. <http://doi.org/10.1016/j.neuroimage.2013.12.044>

Skudlarski, P., Jagannathan, K., Anderson, K., Stevens, M. C., Calhoun, V. D., Skudlarska, B. A., and Pearlson, G. (2010). Brain connectivity is not only lower but different in schizophrenia: A combined anatomical and functional approach. *Biological Psychiatry*, **68**(1), 61–69.

Spagnolo, P. A., and Goldman, D. (2017). Neuromodulation interventions for addictive disorders: challenges, promise, and roadmap for future research. *Brain: A Journal of Neurology*, **140**(5), 1183–1203. <http://doi.org/10.1093/brain/aww284>

Spielberg, J. M., Miller, G. A., Heller, W., and Banich, M. T. (2015). Flexible brain network reconfiguration supporting inhibitory control. *Proceedings of the National Academy of Sciences*, **112**(32), 10020–10025.

Stone, J., Davis, J., Leucht, S., and Pilowsky, L. (2009). Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs: An original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature. *Schizophrenia Bulletin*, **35**(4), 789–797.

Stout, J. C., Busemeyer, J. R., Lin, A., and Grant, S. J. (2004). Bonson KR: Cognitive modeling analysis of decision-making processes in cocaine abusers. *Psychonomic Bulletin and Review*, **11**, 742–747.

Sweet, J. J., Meyer, D. G., Nelson, N. W., and Moberg, P. J. (2011). The TCN/AACN

2010 “salary survey”: Professional practices, beliefs, and incomes of U.S. neuropsychologists. *The Clinical Neuropsychologist*, **25**(1), 12–61.

Tanabe, J., Reynolds, J., Krmpotich, T., Claus, E., Thompson, L. L., Du, Y. P., and Banich, M. T. (2013). Reduced neural tracking of prediction error in substance-dependent individuals. *The American Journal of Psychiatry*, **170**(11), 1356–1363.

Taylor, P. C. J., Walsh, V., and Eimer, M. (2008). Combining TMS and EEG to study cognitive function and cortico–cortico interactions. *Behavioral Brain Research*, **191**, 141–147.

Tovar-Spinoza, Z. S., Ochi, A., Rutka, J. T., Go, C., and Otsubo, H. (2008). The role of magnetoencephalography in epilepsy surgery. *Neurosurgical Focus*, **25**, E16.

Tse, C.-Y., Lee, C.-L., Sullivan, J., Garnsey, S. M., Dell, G. S., Fabiani, M., and Gratton, G. (2007). Imaging cortical dynamics of language processing with the event-related optical signal. *Proceedings of the National Academy of Sciences*, **104**, 17157–17162.

Vaessen, M. J., Saj, A., Lovblad, K.-O., Gschwind, M., and Vuilleumier, P. (2016). Structural white-matter connections mediating distinct behavioral components of spatial neglect in right brain-damaged patients. *Cortex*, **77**, 54–68.

<http://doi.org/10.1016/j.cortex.2015.12.008>

Vallar, G., and Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions: A clinical CT/scale study in man. *Neuropsychologia*, **24**, 609–622.

Voarino, N., Dubljević, V., and Racine, E. (2016). tDCS for memory enhancement: Analysis of the speculative aspects of ethical issues. *Frontiers in Human Neuroscience*, **10**, 678. <http://doi.org/10.3389/fnhum.2016.00678>

von Rhein, D., Beckmann, C. F., Franke, B., Oosterlaan, J., Heslenfeld, D. J., Hoekstra,

P. J., et al. (2017). Network-level assessment of reward-related activation in patients with ADHD and healthy individuals. *Human Brain Mapping*, **38**, 2359–2369.

Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., and Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *The New England Journal of Medicine*, **368**(15), 1388–1397.

Warren, D. E., Power, J. D., Bruss, J., Denburg, N. L., Waldron, E. J., Sun, H., et al. (2014). Network measures predict neuropsychological outcome after brain injury. *Proceedings of the National Academy of Sciences*, **111**(39), 14247–14252.

Wassermann, E. M. (1998). Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalography and Clinical Neurophysiology*, **198**, 1–16.

Wassermann, E. M., Cohen, L. G., Flitman, S. S., Chen, R., and Hallett, M. (1996). Seizure in healthy people with repeated “safe” trains of transcranial magnetic stimulation. *Lancet*, **347**, 825–826.

Wassermann, E. M., and Zimmermann, T. (2012). Transcranial magnetic brain stimulation: Therapeutic promises and scientific gaps. *Pharmacology and Therapeutics*, **133**(1), 98–107.

Wechsler, D. (2008). Wechsler adult intelligence scale, fourth edition. Upper Saddle River, NJ: Pearson Education.

Wechsler, D. (2012). Wechsler preschool and primary scale of intelligence, fourth edition. Upper Saddle River, NJ: Pearson Education.

Wechsler, D. (2014). Wechsler intelligence scale for children, fifth edition. Upper Saddle River, NJ: Pearson Education.

Wechsler, D., and Naglieri, J. A. (2006). Wechsler nonverbal scale of ability. Upper Saddle River, NJ: Pearson Education.

Weigl, W., Milej, D., Janusek, D., Wojtkiewicz, S., Sawosz, P., Kacprzak, M., et al. (2016). Application of optical methods in the monitoring of traumatic brain injury: A review. *Journal of Cerebral Blood Flow and Metabolism*, **36**(11), 1825–1843.

Weintraub, S., Dikmen, S. S., Heaton, R. K., et al. (2013). Cognition assessment using the NIH Toolbox. *Neurology* **80**, S54–S64.

Woo, C.-W., Chang, L. J., Lindquist, M. A., and Wager, T. D. (2017). Building better biomarkers: Brain models in translational neuroimaging. *Nature Neuroscience*, **20**(3), 365–377.

Woo, C.-W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., et al. (2014). Separate neural representations for physical pain and social rejection. *Nature Communications*, **5**, 5380. <http://doi.org/10.1038/ncomms6380>

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, **106**(3), 1125–1165.

Zhang, H., Dong, W., Dang, W., Quan, W., Tian, J., Chen, R., et al. (2015). Near-infrared spectroscopy for examination of prefrontal activation during cognitive tasks in patients with major depressive disorder: A meta-analysis of observational studies. *Psychiatry and Clinical Neurosciences*, **69**(1), 22–33. <http://doi.org/10.1111/pcn.12209>

Chapter 4

Ackermann, H., Mathiak, K., and Riecker, A. (2007). The contribution of the cerebellum to speech production and speech perception: Clinical and functional imaging data. *Cerebellum*, **6**, 202–213.

Albin, R. L., Young, A. B., and Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in Neurosciences*, **12**, 366–375.

Alexander, W. H., and Brown, J. W. (2011). Medial prefrontal cortex as an action-outcome predictor. *Nature Neuroscience*, **14**, 1338–1344.

Amiez, C., and Petrides, M. (2014). Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. *Cerebral Cortex*, **24**(3), 563–578.

Antelis, J. M., Montesano, L., Ramos, A., Birbaumer, N., and Minguez, J. (2016). Decoding upper limb movement attempt from EEG measurements of the contralesional motor cortex in chronic stroke patients. *IEEE Transactions on Bio-Medical Engineering*.

Antonini, A., Vontobel, P. Psylla, M., Günther, I., Maguire, P. R., Missimer, J., and Leenders, K. L. (1995). Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease. *Archives of Neurology*, **52**(12), 1183–1190.

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., and Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, **6**, 115–116.

Aron, A. R., Robbins, T. W., and Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*, **18**(4), 177–185.

Baranauskas, G. (2014). What limits the performance of current invasive brain machine interfaces? *Frontiers in Systems Neuroscience*, **8**, 68.

Bartels, A. L., and Leenders, K. L. (2009). Parkinson's disease: The syndrome, the pathogenesis and pathophysiology. *Cortex*, **45**(8), 915–921.

Bastian, A. J. (2006). Learning to predict the future: The cerebellum adapts feedforward movement control. *Current Opinion in Neurobiology*, **16**, 645–649.

Bastian, A. J., Martin, T. A., Keating, J. G., and Thach, W. T. (1996). Cerebellar ataxia: Abnormal control of interaction torques across multiple joints. *Journal of Neurophysiology*, **76**, 492–509.

Battaglia-Mayer, A., Ferrari-Toniolo, S., and Visco-Comandini, F. (2015). Timing and communication of parietal cortex for visuomotor control. *Current Opinion in Neurobiology*, **33**, 103–109.

Beckmann, M., Johansen-Berg, H., and Rushworth, M. F. S. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *The Journal of Neuroscience*, **29**(4), 1175–1190.

Benabid, A. L., Chabardes, S., Mitrofanis, J., and Pollak, P. (2009). Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Lancet Neurology*, **8**, 67–81.

Bergman, H., and Deuschl, G. (2002). Pathophysiology of Parkinson's disease: From clinical neurology to basic neuroscience and back. *Movement Disorders*, **17**(Suppl. 3), S28–40.

Bernard, J. A., and Mittal, V. A. (2015). Dysfunctional activation of the cerebellum in schizophrenia: A functional neuroimaging meta-analysis. *Clinical Psychological Science: A Journal of the Association for Psychological Science*, **3**(4), 545–566.

Blakemore, S. J., Wolpert, D. M., and Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nature Neuroscience*, **1**, 635–640.

Blangero, A., Menz, M., McNamara, A., and Binkofski, F. (2009). Parietal modules for reaching. *Neuropsychologia*, **47**, 1500–1507.

Bonini, L. (2016). The extended mirror neuron network: anatomy, origin, and functions. *The Neuroscientist*, e-publication in advance of print.

Botvinick, M. M., Cohen, J. D., and Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, **8**(12), 539–546.

Bouton, C. E., Shaikhouni, A., Annetta, N. V., Bockbrader, M. A., Friedenberg, D. A., Nielson, D. M., et al. (2016). Restoring cortical control of functional movement in a human with quadriplegia. *Nature*, **533**(7602), 247–250.

Braak, H., and Del Tredici, K. (2008). Assessing fetal nerve cell grafts in Parkinson's disease. *Nature Medicine*, **14**, 483–485.

Bradshaw, J. L., Phillips, J. G., Dennis, C., Mattingley, J. B., Andrewes, D., Chiu, E., Pierson, J. M., and Bradshaw, J. A. (1992). Initiation and execution of movement sequences in those suffering from and at-risk of developing Huntington's disease. *Journal of Clinical and Experimental Neuropsychology*, **14**, 179–192.

Breska, A., and Ivry, R. B. (2016). Taxonomies of timing: Where does the cerebellum fit in? *Current Opinion in Behavioral Sciences*, **8**, 282–288.

Brinkman, C. (1984). Supplementary motor area of the monkey's cerebral cortex: Short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *Journal of Neuroscience*, **4**, 918–929.

Buccino, G., Lui, F., Canessa, N., Patteri, I., Lagravinese, G., Benuzzi, F., Porro, C. A., and Rizzolatti, G. (2004). Neural circuits involved in the recognition of actions performed by nonconspecifics: An FMRI study. *Journal of Cognitive Neuroscience*, **16**, 114–126.

Buneo, C. A., and Andersen, R. A. (2006). The posterior parietal cortex: Sensorimotor interface for the planning and online control of visually guided movements. *Neuropsychologia*, **44**, 2594–2604.

Buneo, C. A., Jarvis, M. R., Batista, A. P., and Andersen, R. A. (2002). Direct visuomotor transformations for reaching. *Nature*, **416**(6881), 632–636.

Calabresi, P., Picconi, B., Tozzi, A., Ghiglieri, V., and Di Filippo, M. (2014). Direct and indirect pathways of basal ganglia: A critical reappraisal. *Nature Neuroscience*, **17**(8), 1022–1030.

Caretti, V., Stoffers, D., Winogrodzka, A., Isaias, I.-U., Costantino, G., Pezzoli, G., et al. (2008). Loss of thalamic serotonin transporters in early drug-naïve Parkinson's disease patients is associated with tremor: An [(123)I]beta-CIT SPECT study. *Journal of Neural Transmission*, **115**(5), 721–729.

Chambers, C. D., Bellgrove, M. A., Gould, I. C., English, T., Garavan, H., McNaught, E., Kamke, M., and Mattingley, J. B. (2007). Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. *Journal of Neurophysiology*, **98**, 3638–3647.

Chatham, C. H., Claus, E. D., Kim, A., Curran, T., Banich, M. T., and Munakata, Y. (2012). Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. *PLoS ONE*, **7**(2), e31546.

Chaudhary, U., Birbaumer, N., and Curado, M. R. (2015). Brain-machine interface (BMI) in paralysis. *Annals of Physical and Rehabilitation Medicine*, **58**(1), 9–13.

Chikazoe, J., Jimura, K., Asari, T., Yamashita, K., Morimotor, H., Hirose, S., Miyashita, Y., and Konishi, S. (2009). Functional dissociation in right inferior frontal cortex during performance of a go/no-go task. *Cerebral Cortex*, **19**, 146–152.

Chouinard, P. A., and Paus, T. (2006). The primary motor and premotor areas of the

human cerebral cortex. *Neuroscientist*, **12**, 143–152.

Cincotti, F., Mattia, D., Aloise, F., Bufalari, S., Schalk, G., Oriolo, G., Cherubini, A., Marciani, M. G., and Babiloni, F. (2008). Non-invasive brain-computer interface system: Towards its application as assistive technology. *Brain Research Bulletin*, **75**, 796–803.

Cisek, P., and Kalaska, J. F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: Specification of multiple direction choices and final selection of action. *Neuron* **45**(5):801–814.

Clower, W. T., and Alexander, G. E. (1998). Movement sequence-related activity reflecting numerical order of components in supplementary and presupplementary motor areas. *Journal of Neurophysiology*, **80**, 1562–1566.

Connolly, B. S., and Lang, A. E. (2014). Pharmacological treatment of Parkinson disease: A review. *JAMA*, **311**(16), 1670–1683.

Daly, J. J., and Wolpaw, J. R. (2008). Brain-computer interfaces in neurological rehabilitation. *Lancet Neurology*, **7**, 1032–1043.

Dee, H. L., Benton, A. L., and van Allen, M. W. (1970). Apraxia in relation to hemisphere locus of lesion and aphasia. *Transactions of the American Neurological Association*, **95**, 147–148.

Deierborg, T., Soulet, D., Roybon, L., Hall, V., and Brudin, P. (2008). Emerging restorative treatments for Parkinson's disease. *Progress in Neurobiology*, **85**, 407–432.

de La Vega, A., Chang, L. J., Banich, M. T., Wager, T. D., and Yarkoni, T. (2016). Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. *The Journal of Neuroscience*, **36**(24), 6553–6562.

De Renzi, E., and Lucchelli, F. (1988). Ideational apraxia. *Brain*, **111**, 1173–1188.

De Renzi, E., Pieczuro, A., and Vignolo, L. A. (1968). Ideational apraxia: A quantitative study. *Neuropsychologia*, **6**, 41–52.

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., and Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, **2**(6), 563–567.

Desmurget, M., and Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends in Cognitive Sciences*, **4**, 423–443.

Desmurget, M., and Sirigu, A. (2012). Conscious motor intention emerges in the inferior parietal lobule. *Current Opinion in Neurobiology*, **22**(6), 1004–1011.

De Souza, R. A. G., and Leavitt, B. R. (2015). Neurobiology of Huntington's disease. *Current Topics in Behavioral Neurosciences*, **22**, 81–100.

http://doi.org/10.1007/7854_2014_353

Deuschl, G., Toro, C., Zeffiro, T., Massaquoi, S., and Hallett, M. (1996). Adaptation motor learning of arm movements in patients with cerebellar disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **60**, 515–519.

di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., and Rizzolatti, G. (1992). Understanding motor events: A neurophysiological study. *Experimental Brain Research*, **91**(1), 176–180, figures 2 and 3, page 178.

Douaud, G., Gaura, V., Ribeiro, M. J., Lethimonnier, F., Maroy, R., Verny, C., et al. (2006). Distribution of grey matter atrophy in Huntington's disease patients: A combined ROI-based and voxel-based morphometric study. *Neuroimage*, **32**, 1562–1567.

Doyon, J. (2008). Motor sequence learning and movement disorders. *Current Opinion in Neurology*, **21**, 478–483.

Dudman, J. T., and Krakauer, J. W. (2016). The basal ganglia: From motor commands to the control of vigor. *Current Opinion in Neurobiology*, **37**, 158–166.

Duggan, P. S., Siegel, A. W., Blass, D. M., Bok, H., Coyle, J. T., Faden, R., et al. (2009). Unintended changes in cognition, mood, and behavior arising from cell-based interventions for neurological conditions: Ethical challenges. *American Journal of Bioethics*, **9**, 31–36.

Feigin, A., Ghilardi, M. F., Huang, C., Ma, Y., Carbon, M., Guttman, M., Paulsen, J. S., Ghez, C. P., and Eidelberg, D. (2006). Preclinical Huntington's disease: Compensatory brain responses during learning. *Annals of Neurology*, **59**, 53–59.

Filimon, F., Nelson, J. D., Huang, R. S., and Sereno, M. I. (2009). Multiple parietal reach regions in humans: Cortical representations for visual and proprioceptive feedback during on-line reaching. *Journal of Neuroscience*, **29**, 2961–2971.

Foundas, A. L. (2013). Apraxia: Neural mechanisms and functional recovery. *Handbook of Clinical Neurology*, **110**, 335–345.

Fox, C., Ebersbach, G., Ramig, L., and Sapis, S. (2012). LSVT LOUD and LSVT BIG: Behavioral treatment programs for speech and body movement in parkinson disease. *Parkinson's Disease*, **2012**(2), 1–12.

Frank, M. J., Loughry, B., and O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: A computational model. *Cognitive, Affective and Behavioral Neuroscience*, **1**, 136–160.

Frey, S. H., Hansen, M., and Marchal, N. (2015). Grasping with the press of a button: Grasp-selective responses in the human anterior intraparietal sulcus depend on nonarbitrary causal relationships between hand movements and end-effector actions. *Journal of Cognitive Neuroscience*, **27**(6), 1146–1160.

Ganos, C., Roessner, V., and Münchau, A. (2013). The functional anatomy of Gilles de

la Tourette syndrome. *Neuroscience and Biobehavioral Reviews*, **37**(6), 1050–1062.

Georgopoulos, A. P., and Carpenter, A. F. (2015). Coding of movements in the motor cortex. *Current Opinion in Neurobiology*, **33**, 34–39.

Georgopolous, A. P., Lurito, J. T., Petrides, M., Schwartz, A. B., and Massey, J. T. (1989). Mental rotation of the neuronal population vector. *Science*, **243**, 234–236.

Georgopoulos, A. P., Schwartz, A. B., and Kettner, R. E. (1986). Neuronal population coding of movement direction. *Science*, **233**, 1416–1419.

Gerardin, E., Sirigu, A., Lehericy, S., Poline, J. B., Gaymard, B., Marsault, C., Agid, Y., and Le Bihan, D. (2000). Partially overlapping neural networks for real and imagined hand movements. *Cerebral Cortex*, **10**, 1093–1104.

Gerwig, M., Kolb, F. P., and Timmann, D. (2007). The involvement of the human cerebellum in eyeblink conditioning. *Cerebellum*, **6**, 38–57.

Ghosh, R., and Tabrizi, S. J. (2015). Clinical aspects of Huntington's disease. *Current Topics in Behavioral Neuroscience*, **22**, 3–31.

Graybiel, A. M., Aosaki, T., Flaherty, A. W., and Kimura, M. (1994). The basal ganglia and adaptive motor control. *Science*, **265**, 1826–1831.

Graybiel, A. M., and Grafton, S. T. (2015). The striatum: Where skills and habits meet. *Cold Spring Harbor Perspectives in Biology*, **7**(8), a021691.

<http://doi.org/10.1101/cshperspect.a021691>

Graziano, M. S. A. (2016). Ethological action maps: A paradigm shift for the motor cortex. *Trends in Cognitive Sciences*, **20**(2), 121–132.

<http://doi.org/10.1016/j.tics.2015.10.008>

Gross, R. G., and Grossman, M. (2008). Update on apraxia. *Current Neurology and*

Neuroscience Reports, **8**, 490–496.

Halder, S., Varkuti, B., Bogdan, M., Kübler, A., Rosenstiel, W., Sitaram, R., and Birbaumer, N. (2013). Prediction of brain–computer interface aptitude from individual brain structure. *Frontiers in Human Neuroscience*, **7**, 105.

Hampshire, A. (2015). Putting the brakes on inhibitory models of frontal lobe function. *NeuroImage*, **113**, 340–355.

Hartmann, A., and Worbe, Y. (2013). Pharmacological treatment of Gilles de la Tourette syndrome. *Neuroscience and Biobehavioral Reviews*, **37**(6), 1157–1161.

Hauser, T. (1991). *Muhammad Ali: His life and times*. New York: Simon & Schuster.

Heath, M., Roy, E. A., Westwood., D, and Black, S. E. (2001). Patterns of apraxia associated with the production of intransitive limb gestures following left and right hemisphere stroke. *Brain and Cognition*, **46**, 165–169.

Heilman, K. M., and Rothi, L. J. G. (1985). Apraxia. In K. M. Heilman and E. Valenstein (eds.), *Clinical neuropsychology* (2nd edn.) (pp. 131–150). New York: Oxford University Press.

Heilman, K. M., Rothi, L. J., and Valenstein, E. (1982). Two forms of ideomotor apraxia. *Neurology*, **32**, 342–346.

Heimer, G., Rivlin-Etzion, M., Bar-Gad, I., Goldberg, J. A., Haber, S. N., and Bergman, H. (2006). Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of Parkinsonism. *Journal of Neuroscience*, **26**, 8101–8114.

Heiser, M., Iacoboni, M., Maeda, F., Marcus, J., and Mazziotta, J. C. (2003). The essential role of Broca's area in imitation. *European Journal of Neuroscience*, **17**, 1123–1128.

Helmich, R. C., Toni, I., Deuschl, G., and Bloem, B. R. (2013). The pathophysiology of essential tremor and Parkinson's tremor. *Current Neurology and Neuroscience Reports*, **13**(9), 378.

Henley, S. M. D., Wild, E. J., Hobbs, N. Z., Scahill, R. I., Ridgway, G. R., Macmanus, D. G., et al. (2009). Relationship between CAG repeat length and brain volume in premanifest and early Huntington's disease. *Journal of Neurology*, **256**, 203–212.

Hickok, G. (2009). Eight problems for the mirror neuron theory of action understanding in monkeys and humans. *Journal of Cognitive Neuroscience*, **21**(7), 1229–1243.

Hickok, G. (2013). Do mirror neurons subserve action understanding? *Neuroscience Letters*, **540**, 56–58.

Hoekstra, P. J., Anderson, G. M., Limburg, P. C., Korf, J., Kallenberg, C. G., and Minderaa, R. B. (2009). Neurobiology and neuroimmunology of Tourette's syndrome: An update. *Cellular and Molecular Life Sciences*, **61**, 886–898.

Iacoboni, M., and Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nature Reviews Neuroscience*, **7**, 942–951.

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., and Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science*, **286**, 2526–2528.

Ilg, W., and Thier, P. (2008). The neural basis of smooth pursuit eye movements in the rhesus monkey brain. *Brain and Cognition*, **68**, 229–240.

Immisch, I., Waldvogel, D., van Gelderen, P., and Hallett, M. (2001). The role of the medial wall and its anatomical variations for bimanual antiphase and in-phase movements. *NeuroImage*, **14**(3), 674–684.

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nature Reviews Neuroscience*, **9**, 304–313.

Ivry, R. B., and Spencer, R.M. (2004). The neural representation of time. *Current Opinions in Neurobiology*, **14**, 225–232.

Ivry, R. B., Spencer, R. M., Zelaznik, H. N., and Diedrichsen, J. (2002). The cerebellum and event timing. *Annals of the New York Academy of Sciences*, **978**, 302–317.

Jackson, G. M., Draper, A., Dyke, K., Pépés, S. E., and Jackson, S. R. (2015). Inhibition, disinhibition, and the control of action in Tourette syndrome. *Trends in Cognitive Sciences*, **19**(11), 655–665.

Jech, R., Klempír, J., Vymazal, J., Zidovská, J., Klempírová, O., Ružicka, E., and Roth, J. (2007). Variation of selective gray and white matter atrophy in Huntington's disease. *Movement Disorders*, **22**, 1783–1789.

Johnson-Frey, S. H., Newman-Norlund, R., and Grafton, S. T. (2005). A distributed left hemisphere network active during planning of everyday tool use skills. *Cerebral Cortex*, **15**, 681–695.

Kalia, L. V., and Lang, A. E. (2015). Parkinson's disease. *Lancet*, **386**(9996), 896–912.

Karni, A., Meyer, G., Jezard, P., Adams, M. M., Turner, R., and Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, **377**, 155–158.

Karni, A., Meyer, G., Jezard, P., Adams, M. M., Turner, R., and Ungerleider, L. G. (1998). The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences*, **95**, 861–868.

Kilner, J. M., and Lemon, R. N. (2013). What we know currently about mirror neurons. *Current Biology*, **23**(23), R1057–62.

Kuhn, A. A., Kupsch, A., Schneider, G. H., and Brown, P. (2006). Reduction in subthalamic 8–35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *European Journal of Neuroscience*, **23**, 1956–1960.

Kurtzer, I., Herter, T. M., and Scott, S. H. (2005). Random change in cortical load representation suggests distinct control of posture and movement. *Nature Neuroscience*, **8**, 498–504.

Lau, H., Rogers, R. D., Haggard, P., and Passingham, R. E. (2004). Attention to intention. *Science*, **303**, 1208–1210.

Lenneberg, E. H. (1967). *Biological foundations of language*. New York: Wiley.

Leung, H. C., and Cai, W. (2007). Common and differential ventrolateral prefrontal activity during inhibition of hand and eye movements. *Journal of Neuroscience*, **27**, 9893–9900.

Levine, D. N., Kaufman, K. J., and Mohr, J. P. (1978). Inaccurate reaching associated with a superior parietal lobe tumor. *Neurology*, **28**, 556–561.

Lezak, M. D., Howieson, D. B., Bigler, E. D., and Tranel, D. (2012). *Neuropsychological assessment* (5th edn.). Oxford: Oxford University Press.

Liepmann, H. K. (1905). *Ueber Störungen des Handelns bei Gehirnkranke[n]* [On disorders of action involving brain health] Berlin: Karger.

Lindvall, O. (2016). Clinical translation of stem cell transplantation in Parkinson's disease. *Journal of Internal Medicine*, **279**(1), 30–40.

Lipsyte, R. (2016). Muhammad Ali dies at 74: Titan of boxing and the 20th century', *The New York Times*, June 4.

Marras, C. (2015). Subtypes of Parkinson's disease: State of the field and future

directions. *Current Opinion in Neurology*, **28**(4), 382–386.

Marvel, C. L., and Desmond, J. E. (2010). Functional topography of the cerebellum in verbal working memory. *Neuropsychology Review*, **20**(3), 271–279.

Mauk, M. D., Medina, J. F., Nores, W. L., and Ohyama, T. (2000). Cerebellar function: Coordination, learning or timing? *Current Biology*, **10**, R522–R525.

McIntyre, J., Stratta, F., and Lacquaniti, F. (1997). Viewer-centered frame of reference for pointing to memorized targets in three-dimensional space. *Journal of Neurophysiology*, **78**(3), 1601–1618.

Miall, R. C., and Jenkinson, E. W. (2005). Functional imaging of changes in cerebellar activity related to learning during a novel eye-hand tracking task. *Experimental Brain Research*, **166**, 170–183.

Miall, R. C., Reckess, G. Z., and Imamizu, H. (2001). The cerebellum coordinates eye and hand tracking movements. *Nature Neuroscience*, **4**, 638–644.

Middleton, F. A., and Strick, P. L. (2000). Basal ganglia and cerebellar loops: Motor and cognitive circuits. *Brain Research Reviews*, **31**, 236–250.

Milham, M. P., Banich, M. T., Webb, A., Barad, V., Cohen, N. J., Wszalek, T., and Kramer, A. F. (2001). The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Cognitive Brain Research*, **12**, 467–473.

Mink, J. (1996). The basal ganglia: Focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, **50**, 381–425.

Mink, J. W. (2001). Basal ganglia dysfunction in Tourette's syndrome: A new hypothesis. *Pediatric Neurology*, **25**, 190–198.

Mitz, A. R., and Wise, S. P. (1987). The somatotopic organization of the supplementary motor area: Intracortical microstimulation mapping. *Journal of Neuroscience*, **7**, 1010–1021.

Molenberghs, P., Cunnington, R., and Mattingley, J. B. (2012). Brain regions with mirror properties: A meta-analysis of 125 human fMRI studies. *Neuroscience and Biobehavioral Reviews*, **36**(1), 341–349.

Moritz, C. T., Perlmutter, S. I., and Fetz, E. E. (2008). Direct control of paralysed muscles by cortical neurons. *Nature*, **456**, 639–642.

Morton, S. M., and Bastian, A. J. (2004). Cerebellar contributions to balance and locomotion. *Neuroscientist*, **10**, 247–259.

Mountcastle, V. B., Lynch, J. C., Georgopoulos, A., Sakata, H., and Acuna, C. (1975). Posterior parietal association cortex of the monkey: Command functions for operations within extrapersonal space. *Journal of Neurophysiology*, **38**, 871–908.

Mulliken, G. H., Musallam, S., and Andersen, R. A. (2008). Decoding trajectories from posterior parietal cortex ensembles. *Journal of Neuroscience*, **28**, 12913–12926.

Musallam, S., Corneil, B. D., Greger, B., Scherberger, H., and Andersen, R. A. (2004). Cognitive control signals for neural prosthetics. *Science*, **304**, 258–262.

Nachev, P., Kennard, C., and Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, **9**, 856–869.

Narayana, S., Fox, P., Zhang, W., Franklin, C., Robin, D., Vogel, D., and Ramig, L. (2009). Neural correlates of efficacy of voice therapy in Parkinson's disease identified by performance-correlation analysis. *Human Brain Mapping*, **31**, 222–236.

Nicolelis, M. A. L., and Lebedev, M. A. (2009). Principles of neural ensemble

physiology underlying the operation of brain-machine interfaces. *Nature Reviews Neuroscience*, **10**, 530–540.

Niessen, E., Fink, G. R., and Weiss, P. H. (2014). Apraxia, pantomime and the parietal cortex. *NeuroImage. Clinical*, **5**, 42–52.

Olanow, C. W., Stern, M. B., and Sethi, K. (2009). The scientific and clinical basis for the treatment of Parkinson disease. *Neurology*, **72**(Suppl. 4), S1–S136.

Nutt, J. G. (2016). Motor subtype in Parkinson's disease: Different disorders or different stages of disease? *Movement Disorders*, **31**(7), 993–1077.

<http://doi.org/10.1002/mds.26657>

Paschou, P. (2013). The genetic basis of Gilles de la Tourette Syndrome. *Neuroscience and Biobehavioral Reviews*, **37**(6), 1026–1039.

Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., et al. (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery, and Psychiatry*, **79**(8), 874–880.

Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia*, **34**(6), 475–483.

Paus, T. (2001). Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience*, **2**, 417–424.

Paus, T., Kalina, M., Patockova, L., Angerova, Y., Cerny, R., Mecir, P., Bauer, J., and Krabec, P. (1991). Medial versus lateral frontal lobe lesions and differential impairment of central-gaze fixation maintenance in man. *Brain*, **114**, 2051–2067.

Paus, T., Petrides, M., Evans, A. C., and Meyer, E. (1993). Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. *Journal of Neurophysiology*, **70**, 1–18.

Pedersen, J. R., Johannsen, P., Bak, C. K., Kofoed, B., Saermark, K., and Gjedde, A. (1998). Origin of human motor readiness field linked to left middle frontal gyrus by MEG and PET. *NeuroImage*, **8**, 214–220.

Peterson, B. S., Thomas, P., Kane, M. J., Scahill, L., Zhang, H., Bronen, R., King, R. A., Leckman, J. F., and Staib, L. (2003). Basal ganglia volumes in patients with Gilles de la Tourette syndrome. *Archives of General Psychiatry*, **60**, 415–424.

Petreska, B., Adriani, M., Blanke, O., and Billard, A. G. (2007). Apraxia: A review. *Progress in Brain Research*, **164**, 61–83.

Phillips, W., Shannon, K. M., and Barker, R. A. (2008). The current clinical management of Huntington's disease. *Movement Disorders*, **23**, 1491–1504.

Picard, N., and Strick, P. L. (1996). motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, **6**(3), 342–353.

Poeck, K., and Lehmkuhl, G. (1980). Das Syndrom der ideatorischen Apraxie und seine Localisation [Ideational apraxia syndrome and its localization]. *Nervenarzt*, **51**, 217–225.

Procyk, E., Wilson, C. R. E., Stoll, F. M., Faraut, M. C. M., Petrides, M., and Amiez, C. (2016). Midcingulate motor map and feedback detection: Converging data from humans and monkeys. *Cerebral Cortex*, **26**(2), 467–476.

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M. C., Lehericy, S., Bergman, H., et al. (2010). Goal-directed and habitual control in the basal ganglia: Implications for Parkinson's disease. *Nature Reviews Neuroscience*, **11**(11), 760–772.

Rice, N. J., Tunik, E., and Grafton, S. T. (2006). The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: New insights from transcranial magnetic stimulation. *Journal of Neuroscience*, **26**, 8176–8182.

Rivlin-Etzion, M., Marmor, O., Heimer, G., Raz, A., Nini, A., and Bergman, H. (2006). Basal ganglia oscillations and pathophysiology of movement disorders. *Current Opinion in Neurobiology*, **16**, 629–637.

Rizzolatti, G., and Arbib, M. (1998). Language within our grasp. *Trends in Neurosciences*, **21**, 188–194.

Rizzolatti, G., and Fabbri-Destro, M. (2008). The mirror system and its role in social cognition. *Current Opinion in Neurobiology*, **18**, 179–184.

Rizzolatti, G., and Fogassi, L. (2014). The mirror mechanism: Recent findings and perspectives. *Philosophical Transactions of the Royal Society of London, Series B*, **369**(1644), 20130420–20130420.

Roberts, R. E., Bain, P. G., Day, B. L., and Husain, M. (2013). Individual differences in expert motor coordination associated with white matter microstructure in the cerebellum. *Cerebral Cortex*, **23**(10), 2282–2292.

Roland, P. E., Larsen, B., Lassen, N. A., and Skinhøj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of Neurophysiology*, **43**, 118–136.

Rowland, N. C., Sammartino, F., and Lozano, A. M. (2016). Advances in surgery for movement disorders. *Movement Disorders*, e-publication in advance of print.

Rubens, A. B., Geschwind, N., Mahowald, M. W., and Mastri, A. (1977). Posttraumatic cerebral hemispheric disconnection syndrome. *Archives of Neurology*, **34**, 750–755.

Ryu, S. I., and Shenoy, K. V. (2009). Human cortical prostheses: Lost in translation? *Neurological Focus*, **27**, E5.

Sadtler, P. T., Quick, K. M., Golub, M. D., Chase, S. M., Ryu, S. I., Tyler-Kabara, E. C., et al. (2014). Neural constraints on learning. *Nature*, **512**(7515), 423–426.

Schall, J. D., and Boucher, L. (2007). Executive control of gaze by the frontal lobes. *Cognitive, Affective and Behavioral Neuroscience*, **7**, 396–412.

Schiller, P. H., True, S. D., and Conway, J. L. (1980). Deficits in eye movements following frontal eye field and superior colliculus ablations. *Journal of Neurophysiology*, **44**, 1175–1189.

Schlag-Rey, M., Schlag, J., and Dassonville, P. (1992). How the frontal eye field can impose a saccade goal on superior colliculus neurons. *Journal of Neurophysiology*, **67**, 1003–1005.

Schoneburg, B., Mancini, M., Horak, F., and Nutt, J. G. (2013). Framework for understanding balance dysfunction in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, **28**(11), 1474–1482.

Schuepbach, W. M. M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., et al. (2013). Neurostimulation for Parkinson's disease with early motor complications. *The New England Journal of Medicine*, **368**(7), 610–622.

Scott, S. H. (2000). Population vectors and motor cortex: Neural coding or epiphenomenon? *Nature Neuroscience*, **3**, 307–308.

Scott, S. H. (2008). Inconvenient truths about neural processing in primary motor cortex. *Journal of Physiology*, **586**, 1217–1224.

Scott, S. H. (2012). The computational and neural basis of voluntary motor control and planning. *Trends in Cognitive Sciences*, **16**(11), 541–549.

Shadmehr, R., and Krakauer, J. W. (2008). A computational neuroanatomy for motor control. *Experimental Brain Research*, **185**, 359–381.

Shakiba, A. (2014). The role of the cerebellum in neurobiology of psychiatric

disorders. *Neurologic Clinics*, **32**(4), 1105–1115.

Shima, K., and Tanji, J. (2000). Neuronal activity in the supplementary and presupplementary motor areas for temporal organization of multiple movements. *Journal of Neurophysiology*, **84**, 2148–2160.

Sirigu, A., Duhamel, J.-R., Cohen, L., Pillon, B., Dubois, B., and Agid, Y. (1996). The mental representation of hand movements after parietal cortex damage. *Science*, **273**, 1564–1568.

Soekadar, S. R., Birbaumer, N., Slutzky, M. W., and Cohen, L. G. (2015). Brain-machine interfaces in neurorehabilitation of stroke. *Neurobiology of Disease*, **83**, 172–179. <http://doi.org/10.1016/j.nbd.2014.11.025>

Spencer, K. A., and Slocumb, D. L. (2007). The neural basis of ataxic dysarthria. *Cerebellum*, **6**, 58–65.

Starkstein, S. E., Brandt, J., Folstein, S., Strauss, M., Berthier, M. L., Pearlson, G. D., et al. (1988). Neuropsychological and neuroradiological correlates in Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 1259–1263.

Sternberg, S. S., Monsell, S., Knoll, R. L., and Wright, C. E. (1978). The latency and duration of rapid movement sequences: Comparisons of speech and type-writing. In G. E. Stelmach (ed.), *Information processing in motor control and learning* (pp. 118–152). New York: Academic Press.

Stevens, M. C., Kiehl, K. A., Pearlson, G. D., and Calhoun, V. D. (2009). Brain networks during error commission. *Human Brain Mapping*, **30**, 24–37.

Stoodley, C. J. (2016). The cerebellum and neurodevelopmental disorders. *Cerebellum*, **15**(1), 34–37.

Stoodley, C. J., and Schmahmann, J. D. (2009). Functional topography in the human

cerebellum: A meta-analysis of neuroimaging studies. *Neuroimage*, **44**, 489–501.

Swann, N. C., Cai, W., Conner, C. R., Pieters, T. A., Claffey, M. P., George, J. S., et al. (2012). Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: Electrophysiological responses and functional and structural connectivity. *NeuroImage*, **59**(3), 2860–2870.

Tanji, J., and Shima, K. (1994). Role for supplementary motor area cells in planning several movements ahead. *Nature*, **371**, 413–416.

Tanji, J., Taniguchi, K., and Saga, T. (1980). Supplementary motor area: Neuronal response to motor instructions. *Journal of Neurophysiology*, **43**, 60–68.

Taylor, S. F., Stern, E. R., and Gehring, W. J. (2007). Neural systems for error monitoring: recent findings and theoretical perspectives. *The Neuroscientist*, **13**(2), 160–172. <http://doi.org/10.1177/1073858406298184>

Thach, W. T. (2014). Does the cerebellum initiate movement? *Cerebellum*, **13**(1), 139–150.

Tian, J. R., Zee, D. S., Lasker, A. G., and Folstein, S. E. (1991). Saccades in Huntington's disease: Predictive tracking and interaction between release of fixation and initiation of saccades. *Neurology*, **41**, 875–881.

Turner, R. S., and Desmurget, M. (2010). Basal ganglia contributions to motor control: A vigorous tutor. *Current Opinion in Neurobiology*, **20**(6), 704–716.

Utter, A. A., and Basso, M. A. (2008). The basal ganglia: An overview of circuits and function. *Neuroscience and Biobehavioral Reviews*, **32**, 333–342.

Vernet, M., Quentin, R., Chanes, L., Mitsumasu, A., and Valero-Cabré, A. (2014). Frontal eye field, where art thou? Anatomy, function, and non-invasive manipulation of frontal regions involved in eye movements and associated cognitive operations.

Frontiers in Integrative Neuroscience, **8**, 66.

Vesia, M., and Crawford, J. D. (2012). Specialization of reach function in human posterior parietal cortex. *Experimental Brain Research*, **221**(1), 1–18.

Vogt, B. A., Finch, D. M., and Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: The anterior executive and posterior evaluative regions. *Cerebral Cortex*, **2**, 435–443.

Voigt, M., and Klausen, K. (1990). Changes in muscle strength and speed of an unloaded movement after various training programmes. *European Journal of Applied Physiology and Occupational Physiology*, **60**, 370–376.

Waldvogel, H. J., Kim, E. H., Thu, D. C. V., Tippet, L. J., and Faull, R. L. M. (2012). New perspectives on the neuropathology in Huntington's disease in the human brain and its relation to symptom variation. *Journal of Huntington's Disease*, **1**(2), 143–153.

Wessberg, J., Stambaugh, C. R., Kralik, J. D., Beck, P. D., Laubach, M., Chapin, J. K., Kim, J., Biggs, S. J., Srinivasan, M. A., and Nicolelis, M. A. (2000). Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. *Nature*, **408**, 361–365.

Westwood, D. A., Schweizer, T. A., Heath, M. D., Roy, E. A., Dixon, M. J., and Black, S. (2001). Transitive gesture production in apraxia: Visual and nonvisual sensory contributions. *Brain and Cognition*, **46**, 300–304.

Wichmann, T., and Soares, J. (2006). Neuronal firing before and after burst discharges in the monkey basal ganglia is predictably patterned in the normal state and altered in Parkinsonism. *Journal of Neurophysiology*, **95**, 2120–2133.

Wisneski, K. J., Anderson, N., Schalk, G., Smyth, M., Moran, D., and Leuthardt, E. C. (2008). Unique cortical physiology associated with ipsilateral hand movements and neuroprosthetic implications. *Stroke*, **39**, 3351–3359.

Wolpert, D. M., Diedrichsen, J., and Flanagan, J. R. (2011). Principles of sensorimotor learning. *Nature Reviews Neuroscience*, **12**(12), 739–751.

Zangwill, O. L. (1960). La problème de l'apraxie idéatoire [The problem of ideational apraxia]. *Revue Neurologique (Paris)*, **102**, 595–603.

Zhuang, P., Hallett, M., Zhang, X., Li, J., Zhang, Y., Li, Y. (2009). Neuronal activity in the globus pallidus internus in patients with tics. *Journal of Neurology, Neurosurgery Psychiatry*, **80**, 1075–1081.

Zigmond, M. J., Abercrombie, E. D., Berger, T. W., Grace, A. A., et al. (1990). Compensations after lesions of central dopaminergic neurons: Some clinical and basic implications. *Trends in Neurosciences*, **13**, 290–296.

Chapter 5

Ahveninen, J., Huang, S., Nummenmaa, A., Belliveau, J. W., Hung, A. Y., Jääskeläinen, I. P., and Raij, T. (2013). Evidence for distinct human auditory cortex regions for sound location versus identity processing. *Nature Communications*, **4**, 2585.

Ahveninen, J., Jääskeläinen, I. P., Raij, T., Bonmassar, G., Devore, S., Hämäläinen, M., et al. (2006). Task modulated “what” and “where” pathways in human auditory cortex. *Proceedings of the National Academy of Sciences*, **103**, 14608–14613.

Ajina, S., Pestilli, F., Rokem, A., Kennard, C., and Bridge, H. (2015). Human blindsight is mediated by an intact geniculo-extrastriate pathway. *eLife*, **4**, e08935.

Atiani, S., David, S. V., Elgueda, D., Locastro, M., Radtke-Schuller, S., Shamma, S. A., and Fritz, J. B. (2014). Emergent selectivity for task-relevant stimuli in higher-order auditory cortex. *Neuron*, **82**, 486–499.

Azzi, J. C., Gattass, R., Lima, B., Soares, J. G., and Fiorani, M. (2015). Precise visuotopic organization of the blind spot representation in primate V1. *Journal of Neurophysiology*, **113**, 3588–3599.

Bartels, A., and Zeki, S. (2000). The architecture of the colour centre in the human visual brain: New results and a review. *European Journal of Neuroscience*, **12**, 172–193.

Bell, A. H., Pasternak, T., and Ungerleider, L. G. (2014). Ventral and dorsal cortical processing streams. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Berman, R. A., and Wurtz, R. H. (2011). Signals conveyed in the pulvinar pathway from superior colliculus to cortical area MT. *Journal of Neuroscience*, **31**, 373–384.

Berson, D. M. (2014). Intrinsically photosensitive retinal ganglion cells. In J. S. Werner

and L. M. Chalupa (eds.), The new visual neurosciences. Cambridge, MA: MIT Press.

Bouvier, S. E., and Engel, S. A. (2006). Behavioral deficits and cortical damage loci in cerebral achromatopsia. *Cerebral Cortex*, **16**, 183–191.

Bridge, H., Hicks, S. L., Xie, J., Okell, T. W., Mannan, S., Alexander, I., Kennard, C., et al. (2010). Visual activation of extra-striate cortex in the absence of V1 activation. *Neuropsychologia*, **48**, 4148–4154.

Briggs, F., and Usrey, M. (2014). Functional properties of cortical feedback to the primate lateral geniculate nucleus. In J. S. Werner and L. M. Chalupa (eds.), The new visual neurosciences. Cambridge, MA: MIT Press.

Cohen, Y. E., and Knudsen, H. I. (1999). Maps versus clusters: Different representations of auditory space in the midbrain and forebrain. *Trends in Neuroscience*, **22**, 128–135.

Conway, B. R., Moeller, S., and Tsao, D. Y. (2007). Specialized color modules in macaque extrastriate cortex. *Neuron*, **56**, 560–573.

David, S. V., Hayden, B. Y., and Gallant, J. L. (2006). Spectral receptive field properties explain shape selectivity in area V4. *Journal of Neurophysiology*, **96**, 3492–3505.

Demb, J. B. (2007). Cellular mechanisms for direction selectivity in the retina. *Neuron*, **55**, 179–186.

Dhamala, M., Assisi, C. G., Jirsa, V. K., Steinberg, F. L., and Kelso, J. A. S. (2007). Multisensory integration for timing engages different brain networks. *Neuroimage*, **34**, 764–773.

Falchier, A., Clavagnier, S., Barone, P., and Kennedy, H. (2002). Anatomical evidence of multimodal integration in primate striate cortex. *Journal of Neuroscience*, **22**, 5749–5759.

Felleman, D. J., and van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*, **1**, 1–47.

Feng, W., Störmer, V. S., Martinez, A., McDonald, J. J., and Hillyard, S. A. (2014). Sounds activate visual cortex and improve visual discrimination. *Journal of Neuroscience*, **34**, 9817–9824.

Flevaris, A. V., and Murray, S. O. (2015). Attention determines contextual enhancement versus suppression in human primary visual cortex. *Journal of Neuroscience*, **35**, 12273–12280.

Freeman, R. D. (2014). The cortical organization of binocular vision. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Freeman, J., Ziemba, C. M., Heeger, D. J., Simoncelli, E. P., and Movshon, J. A. (2013). A functional and perceptual signature of the second visual area in primates. *Nature neuroscience*, **16**(7), 974–981.

Gegenfurtner, K. R., and Kiper, D. C. (2004). The processing of color in extrastriate cortex. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp. 1017–1028). Cambridge, MA: MIT Press.

Ghazanfar, A. A., Maier, J. X., Hoffman, K. L., and Logothetis, N. K. (2005). Multisensory integration of dynamic faces and voices in rhesus monkey auditory cortex. *Journal of Neuroscience*, **25**, 5004–5012.

Ghose, D., Maier, A., Nidiffer, A., and Wallace, M. T. (2014). Multisensory response modulation in the superficial layers of the superior colliculus. *Journal of Neuroscience*, **34**, 4332–4344.

Gilbert, C. D., and Li, W. (2013). Top-down influences on visual processing. *Nature Reviews Neuroscience*, **14**, 350–363.

Goodale, M. A., and Westwood, D. A. (2004). An evolving view of duplex vision: Separate but interacting cortical pathways for perception and action. *Current Opinion in Neurobiology*, **14**, 203–211.

Griffiths, T. D., and Warren, J. D. (2002). The planum temporale as a computational hub. *Trends in Neurosciences*, **25**, 348–353.

Hackett, T. A., and Kaas, J. H. (2004). Auditory cortex in primates: Functional subdivisions and processing streams. In M. S. Gazzaniga (ed.), *The cognitive neurosciences III* (pp. 215–232). Cambridge, MA: MIT Press.

Hadjikhani, N., Liu, A. K., Dale, A. M., Cavanagh, P., and Tootell, R. B. (1998). Retinotopy and color sensitivity in human visual cortical area V8. *Nature neuroscience*, **1**(3), 235–241.

Hegd , J., and van Essen, D. C. (2005). Role of primate visual area V4 in the processing of 3-D shape characteristics defined by disparity. *Journal of Neurophysiology*, **94**, 2856–2866.

Hubel, D. H. (1982). Exploration of the primary visual cortex, 1955–78. *Nature*, **299**, 515–524.

Kaas, J. H., Hackett, T. A., and Tramo, M. J. (1999). Auditory processing in primate cerebral cortex. *Current Opinion in Neurobiology*, **9**, 164–170.

Kandel, E. R. (2009). An introduction to the work of David Hubel and Torsten Wiesel. *Journal of Physiology*, **587**, 2733–2741.

Kastner, S., Schneider, K. A., and Wunderlich, K. (2006). Beyond a relay nucleus: Neuroimaging views on the human LGN. *Progress in Brain Research*, **155**, 125–143.

Komatsu, H. (2006). The neural mechanisms of perceptual filling-in. *Nature Reviews*

Neuroscience, **7**, 220–231.

Konishi, M. (2003). Coding of auditory space. *Annual Review of Neuroscience*, **26**, 31–55.

Krauzlis, R.J. (2014). Superior colliculus and visual attention. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Kus'mierek, P., and Rauschecker, J. P. (2014). Selectivity for space and time in early areas of the auditory dorsal stream in the rhesus monkey. *Journal of Neurophysiology*, **111**, 1671–1685.

Kusunoki, M., Moutoussis, K., and Zeki, S. (2006). Effect of background colors on the tuning of color-selective cells in monkey area V4. *Journal of Neurophysiology*, **95**, 3047–3059.

Lafer-Sousa, R., Conway, B. R., and Kanwisher, N. G. (2016). Color-biased regions of the ventral visual pathway lie between face- and place-selective regions in humans, as in macaques. *Journal of Neuroscience*, **36**, 1682–1697.

Lamme, V. A. (2004). Beyond the classical receptive field: Contextual modulation of V1 responses. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp. 720–732). Cambridge, MA: MIT Press.

Leh, S. E., Johansen-Berg, H., and Ptito, A. (2006). Unconscious vision: New insights into the neuronal correlate of blindsight using diffusion tractography. *Brain*, **129**, 1822–1832.

Leh, S. E., Mullen, K. T., and Ptito, A. (2006). Absence of S-cone input in human blindsight following hemispherectomy. *European Journal of Neuroscience*, **24**, 2954–2960.

Li, M., Liu, F., Juusola, M., and Tang, S. (2014). Perceptual color map in macaque

visual area V4. *Journal of Neuroscience*, **34**, 202–217.

Li, P., Zhu, S., Chen, M., Han, C., Xu, H., Hu, J., Lu, H. D., et al. (2013). A motion direction preference map in monkey V4. *Neuron*, **78**, 376–388.

Marois, R., Leung, H.-C., and Gore, J. C. (2000). A stimulus-driven approach to object identity and location processing in the human brain. *Neuron*, **25**, 717–728.

Masland, R. H. (2004). Direction selectivity in retinal ganglion cells. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp. 451–462). Cambridge, MA: MIT Press.

Matsumoto, M., and Komatsu, H. (2005). Neural responses in the macaque V1 to bar stimuli with various lengths presented on the blind spot. *Journal of Neurophysiology*, **93**, 2374–2387.

Meng, M., Remus, D. A., and Tong, F. (2005). Filling-in of visual phantoms in the human brain. *Nature Neuroscience*, **8**, 1248–1254.

Mishkin, M., Ungerleider, G., and Macko, K. A. (1983). Object vision and spatial vision: Two cortical pathways. *Trends in Neurosciences*, **6**, 414–417.

O'Connor, D. H., Fukui, M. M., Pinsk, M. A., and Kastner, S. (2002). Attention modulates responses in the human lateral geniculate nucleus. *Nature Neuroscience*, **5**, 1203–1209.

Ortiz-Rios, M., Kus'mierek, P., DeWitt, I., Archakov, D., Azevedo, F. A., Sams, M., Rauschecker, J. P., et al. (2015). Functional MRI of the vocalization-processing network in the macaque brain. *Frontiers in Neuroscience*, **9**.

Parker, A. J. (2014). Cortical pathways for binocular depth. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Pearson, J., and Westbrook, F. (2015). Phantom perception: Voluntary and involuntary nonretinal vision. *Trends in Cognitive Sciences*, **19**, 278–284.

Pena, J. L., and Gutfreund, Y. (2014). New perspectives on the owl's map of auditory space. *Current Opinion in Neurobiology*, **24**, 55–62.

Petkov, C. I., Kayser, C., Steudel, T., Whittingstall, K., Augath, M., and Logothetis, N. K. (2008). A voice region in the monkey brain. *Nature Neuroscience*, **11**, 367–374.

Polonsky, A., Blake, R., Braun, J., and Heeger, D. J. (2000). Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. *Nature Neuroscience*, **3**, 1153–1159.

Rauschecker, J. P. (2015). Auditory and visual cortex of primates: A comparison of two sensory systems. *European Journal of Neuroscience*, **41**, 579–585.

Recanzone, G. H., and Sutter, M. L. (2008). The biological basis of audition. *Annual Review of Psychology*, **59**, 119–142.

Roe, A. W., Chelazzi, L., Connor, C. E., Conway, B. R., Fujita, I., Gallant, J. L., Vanduffel, W., et al. (2012). Toward a unified theory of visual area V4. *Neuron*, **74**(1), 12–29.

Romanski, L. M. (2012). Integration of faces and vocalizations in ventral prefrontal cortex: Implications for the evolution of audiovisual speech. *Proceedings of the National Academy of Sciences*, **109**, 10717–10724.

Romanski, L. M., and Averbeck, B. B. (2009). The primate cortical auditory system and neural representation of conspecific vocalizations. *Annual Review of Neuroscience*, **32**, 315–346.

Roska, B., and Meister, M. (2014). The retina dissects the visual scene into distinct features. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*.

Cambridge, MA: MIT Press.

Sanes, J. R., and Masland, R. H. (2015). The types of retinal ganglion cells: Current status and implications for neuronal classification. *Annual Review of Neuroscience*, **38**, 221–246.

Schiller, P. H., Logothetis, N. K., and Charles, E. R. (1990). Functions of the colour-opponent and broad-band channels of the visual system. *Nature*, **343**, 68–70.

Schmidt, T. M., Chen, S. K., and Hattar, S. (2011). Intrinsically photosensitive retinal ganglion cells: Many subtypes, diverse functions. *Trends in Neurosciences*, **34**, 572–580.

Schnupp, J. W. H., and Carr, C. E. (2009). On hearing with more than one ear: Lessons from evolution. *Nature Neuroscience*, **12**, 692–697.

Sherman, S. M., and Guillery, R. W. (2014). The lateral geniculate nucleus and pulvinar. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Sillito, A. M., and Jones, H. E. (2004). Feedback systems in visual processing. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp.609–624). Cambridge, MA: MIT Press.

Sincich, L. C., Park, K. F., Wohlgemuth, M. J., and Horton, J. C. (2004). Bypassing Vi: A direct geniculate input to area MT. *Nature Neuroscience*, **7**, 1123–1128.

Spillmann, L., Otte, T., Hamburger, K., and Magnussen, S. (2006). Perceptual filling-in from the edge of the blind spot. *Vision Research*, **46**, 4252–4257.

Stanford, T. R., Quessy, S., and Stein, B. E. (2005). Evaluating the operations underlying multisensory integration in the cat superior colliculus. *Journal of Neuroscience*, **25**, 6499–6508.

Sugihara, T., Diltz, M. D., Averbeck, B. B., and Romanski, L. M. (2006). Integration of auditory and visual communication information in the primate ventrolateral prefrontal cortex. *Journal of Neuroscience*, **26**, 11138–11147.

Tamietto, M., Cauda, F., Corazzini, L. L., Savazzi, S., Marzi, C. A., and Goebel, R. (2010). Collicular vision guides nonconscious behavior. *Journal of Cognitive Neuroscience*, **22**, 888–902.

Tanigawa, H., Lu, H. D., and Roe, A. W. (2010). Functional organization for color and orientation in macaque V4. *Nature Neuroscience*, **13**, 1542–1548.

Tian, B., Reser, D., Durham, A., Kustov, A., and Rauschecker, J. P. (2001). Functional specialization in rhesus monkey auditory cortex. *Science*, **292**, 290–293.

Tong, F., and Engel, S. (2001). Interocular rivalry revealed in the human cortical blind spot representation. *Nature*, **411**, 195–199.

Ts'o, D. Y., Zarella, M., and Burkitt, G. (2009). Whither the hypercolumn? *Journal of Physiology*, **587**, 2791–2805.

Wandell, B. A., and Wade, A. R. (2003). Functional imaging of the visual pathways. *Neurologic Clinics of North America*, **21**, 417–443.

Wandell, B. A., and Winawer, J. (2015). Computational neuroimaging and population receptive fields. *Trends in Cognitive Sciences*, **19**, 349–357.

Wang, Y., Celebrini, S., Trotter, Y., and Barone, P. (2008). Visuo-auditory interactions in the primary visual cortex of the behaving monkey: Electrophysiological evidence. *BMC Neuroscience*, **9**, 79.

Weiskrantz, L. (2004). Blindsight. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp. 657–669). Cambridge, MA: MIT Press.

Weiskrantz, L. (2009). *Blindsight: A case study spanning 35 years and new developments* (2nd edn.). Oxford: Oxford University Press.

Werner, J. S., and Chalupa, L. M. (eds.) (2014). *The new visual neurosciences*. Cambridge, MA: MIT Press.

Woods, D. L., Herron, T. J., Cate, A. D., Yund, E. W., Stecker, G. C., Rinne, T., and Kang, X. (2010). Functional properties of human auditory cortical fields. *Frontiers in Systems Neuroscience*, **4**, 155.

Wurtz, R. H. (2009). Recounting the impact of Hubel and Wiesel. *Journal of Physiology*, **587**, 2817–2823.

Xu, H., Han, C., Chen, M., Li, P., Zhu, S., Fang, Y., Lu, H. D., et al. (2016). Rivalry-like neural activity in primary visual cortex in anesthetized monkeys. *Journal of Neuroscience*, **36**, 3231–3242.

Zachariou, V., Klatzky, R., and Behrmann, M. (2014). Ventral and dorsal visual stream contributions to the perception of object shape and object location. *Journal of Cognitive Neuroscience*, **26**, 189–209.

Zeki, S. (1973). Colour coding in rhesus monkey prestriate cortex. *Brain Research*, **53**, 422–427.

Zeki, S. (1983). Colour coding in the cerebral cortex: The responses of wavelength-selective and colour-coded cells in monkey visual cortex to changes in wavelength composition. *Neuroscience*, **9**, 767–781.

Chapter 6

Afraz, A., Boyden, E. S., and DiCarlo, J. J. (2015). Optogenetic and pharmacological suppression of spatial clusters of face neurons reveal their causal role in face gender discrimination. *Proceedings of the National Academy of Sciences*, **112**, 6730–6735.

Afraz, S.-R., Kiani, R., and Esteky, H. (2006). Microstimulation of inferotemporal cortex influences face categorization. *Nature*, **442**, 692–695.

Albers, A. M., Kok, P., Toni, I., Dijkerman, H. C., and de Lange, F. P. (2013). Shared representations for working memory and mental imagery in early visual cortex. *Current Biology*, **23**, 1427–1431.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., and Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cerebral Cortex*, **12**, 1202–1212.

Amedi, A., Malach, R., Hendler, T., Peled, S., and Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. *Nature Neuroscience*, **4**, 324–330.

Anzellotti, S., and Caramazza, A. (2014). The neural mechanisms for the recognition of face identity in humans. *Frontiers in Psychology*, **5**, 672.

Anzellotti, S., and Caramazza, A. (2016). From parts to identity: Invariance and sensitivity of face representations to different face halves. *Cerebral Cortex*, **26**, 1900–1909.

Avidan, G., Tanzer, M., Hadj-Bouziane, F., Liu, N., Ungerleider, L. G., and Behrmann, M. (2014). Selective dissociation between core and extended regions of the face processing network in congenital prosopagnosia. *Cerebral Cortex*, **24**, 1565–1578.

Axelrod, V., and Yovel, G. (2012). Hierarchical processing of face viewpoint in human

visual cortex. *Journal of Neuroscience*, **32**, 2442–2452.

Baker, C. I., Behrmann, M., and Olson, C. R. (2002). Impact of learning on representation of parts and wholes in monkey inferotemporal cortex. *Nature Neuroscience*, **5**, 1210–1216.

Barlow, H. B. (1985). The twelfth Bartlett Memorial Lecture: The role of single neurons in the psychology of perception. *Quarterly Journal of Experimental Psychology*, **37A**, 121–145.

Behrmann, M., and Avidan, G. (2005). Congenital prosopagnosia: Face-blind from birth. *Trends in Cognitive Sciences*, **9**, 180–187.

Behrmann, M., and Ewell, C. (2003). Expertise in tactile pattern recognition. *Psychological Science*, **14**, 480–486.

Behrmann, M., Moscovitch, M., and Winocur, G. (1994). Intact visual imagery and impaired visual perception in a patient with visual agnosia. *Journal of Experimental Psychology: Human Perception and Performance*, **20**, 1068–1087.

Behrmann, M., Peterson, M. A., Moscovitch, M., and Suzuki, S. (2006). Independent representation of parts and the relations between them: Evidence from integrative agnosia. *Journal of Experimental Psychology: Human Perception and Performance*, **32**, 1169–1184.

Behrmann, M., and Plaut, D. C. (2013). Distributed circuits, not circumscribed centers, mediate visual recognition. *Trends in Cognitive Sciences*, **17**, 210–219.

Belin, P., Zatorre, R. J., Lafaille, P., Ahad, P., and Pike, B. (2000). Voice-selective areas in human auditory cortex. *Nature*, **403**, 309–312.

Berger, C. C., and Ehrsson, H. H. (2014). The fusion of mental imagery and sensation in the temporal association cortex. *Journal of Neuroscience*, **34**, 13684–13692.

Bergmann, J., Genç, E., Kohler, A., Singer, W., and Pearson, J. (2015). Smaller primary visual cortex is associated with stronger, but less precise mental imagery. *Cerebral Cortex*, e-publication ahead of print.

Bestelmeyer, P. E., Belin, P., and Grosbras, M. H. (2011). Right temporal TMS impairs voice detection. *Current Biology*, **21**, R838–R839.

Bobes, M. A., Lopera, F., Diaz Comas, L., Galan, L., Carbonell, F., Bringas, M. L., and Valdes-Sosa, M. (2004). Brain potentials reflect residual face processing in a case of prosopagnosia. *Cognitive Neuropsychology*, **21**, 691–718.

Bornstein, B. (1963). Prosopagnosia. In L. Hapern (ed.), *Problems of dynamic neurology* (pp. 283–318). Jerusalem: Hadassah Medical School.

Bornstein, B., Sroka, M., and Munitz, H. (1969). Prosopagnosia with animal face agnosia. *Cortex*, **5**, 164–169.

Bouhali, F., de Schotten, M. T., Pinel, P., Poupon, C., Mangin, J. F., Dehaene, S., and Cohen, L. (2014). Anatomical connections of the visual word form area. *Journal of Neuroscience*, **34**, 15402–15414.

Bruyer, R., Laterre, C., Seron, X., Feyereisen, P., Strypstein, E., Pierrard, E., and Rectem, D. (1983). A case of prosopagnosia with some preserved covert remembrance of familiar faces. *Brain and Cognition*, **2**, 257–284.

Bukach, C. M., Gauthier, I., and Tarr, M. J. (2006). Beyond faces and modularity: The power of an expertise framework. *Trends in Cognitive Sciences*, **10**, 159–166.

Busey, T. A., and Vanderkolk, J. R. (2005). Behavioral and electrophysiological evidence for configural processing in fingerprint experts. *Vision Research*, **45**, 431–448.

Capitani, E., Laiacona, M., Mahon, B., and Caramazza, A. (2003). What are the facts of

semantic category-specific deficits? A critical review of the clinical evidence. *Cognitive Neuropsychology*, **20**, 213–261.

Caramazza, A., and Mahon, B. Z. (2003). The organization of conceptual knowledge: The evidence from category-specific semantic deficits. *Trends in Cognitive Sciences*, **7**, 354–361.

Cichy, R. M., Heinzle, J., and Haynes, J. D. (2012). Imagery and perception share cortical representations of content and location. *Cerebral Cortex*, **22**, 372–380.

Coggan, D. D., Liu, W., Baker, D. H., and Andrews, T. J. (2016). Category-selective patterns of neural response in the ventral visual pathway in the absence of categorical information. *NeuroImage*, **135**, 107–114.

Cox, D. D., and DiCarlo, J. J. (2008). Does learned shape selectivity in inferior temporal cortex automatically generalize across retinal position? *Journal of Neuroscience*, **28**, 10045–10055.

Daselaar, S. M., Porat, Y., Huijbers, W., and Pennartz, C. M. (2010). Modality-specific and modality-independent components of the human imagery system. *Neuroimage*, **52**, 677–685.

Davies-Thompson, J., Newling, K., and Andrews, T. J. (2013). Image-invariant responses in face-selective regions do not explain the perceptual advantage for familiar face recognition. *Cerebral Cortex*, **23**, 370–377.

De Haan, E. H., Young, A., and Newcombe, F. (1987). Faces interfere with name classification in a prosopagnosic patient. *Cortex*, **23**, 309–316.

Dehaene, S., and Cohen, L. (2011). The unique role of the visual word form area in reading. *Trends in Cognitive Sciences*, **15**, 254–262.

Dehaene, S., Le Clec'H, G., Poline, J. B., Le Bihan, D., and Cohen, L. (2002). The

visual word form area: A prelexical representation of visual words in the fusiform gyrus. *Neuroreport*, **13**, 321–325.

Dehaene, S., Pegado, F., Braga, L. W., Ventura, P., Nunes Filho, G., Jobert, A., Cohen, L., et al. (2010). How learning to read changes the cortical networks for vision and language. *Science*, **330**, 1359–1364.

De Renzi, E. (1986). Current issues in prosopagnosia. In H. D. Ellis, M. A. Jeeves, F. Newcombe, and A. Young (eds.), *Aspects of face processing*. Dordrecht, The Netherlands: Martinus Nijhoff.

Desimone, R., and Gross, C. G. (1979). Visual areas in the temporal cortex of the macaque. *Brain Research*, **178**, 363–380.

Devinsky, O., Farah, M. J., and Barr, W. B. (2008). Visual agnosia. *Handbook of Clinical Neurology*, **88**, 417–427.

Diamond, R., and Carey, S. (1986). Why faces are and are not special: An effect of expertise. *Journal of Experimental Psychology: General*, **115**, 107–117.

DiCarlo, J. J., and Cox, D. D. (2007). Untangling invariant object recognition. *Trends in Cognitive Sciences*, **11**, 333–341.

DiCarlo, J. J., and Maunsell, J. H. R. (2003). Anterior inferotemporal neurons of monkeys engaged in object recognition can be highly sensitive to object retinal position. *Journal of Neurophysiology*, **89**, 3264–3287.

DiCarlo, J. J., Zoccolan, D., and Rust, N. C. (2012). How does the brain solve visual object recognition? *Neuron*, **73**, 415–434.

Dumoulin, S. O., and Wandell, B. A. (2008). Population receptive field estimates in human visual cortex. *Neuroimage*, **39**, 647–660.

Edwards, R., Xiao, D., Keyzers, C., Földiák, P., and Perrett, D. (2003). Color sensitivity of cells responsive to complex stimuli in the temporal cortex. *Journal of Neurophysiology*, **90**, 1245–1256.

Eimer, M., Gosling, A., and Duchaine, B. (2012). Electrophysiological markers of covert face recognition in developmental prosopagnosia. *Brain*, **135**, 542–554.

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences*, **12**, 388–396.

Erez, J., Cusack, R., Kendall, W., and Barense, M. D. (2016). Conjunctive coding of complex object features. *Cerebral Cortex*, **26**, 2271–2282.

Farah, M. J. (1988). Is visual imagery really visual? Overlooked evidence from neuropsychology. *Psychological Review*, **95**, 307–317.

Farah, M. J. (2000). *The cognitive neuroscience of vision*. Malden, MA: Blackwell Publishers.

Farah, M. J. (2004). *Visual agnosia* (2nd edn.). Cambridge, MA: MIT Press.

Farah, M. J., and Feinberg, T. E. (2006). *Patient-based approaches to cognitive neuroscience* (2nd edn.). Cambridge, MA: MIT Press.

Farah, M. J., Levine, D. N., and Calvanio, R. (1988). A case study of a mental imagery deficit. *Brain and Cognition*, **8**, 147–164.

Feinberg, T. E., Schindler, R. J., Ochoa, E., Kwan, P. C., and Farah, M. J. (1994). Associative visual agnosia and alexia without prosopagnosia. *Cortex*, **30**, 395–411.

Freiwald, W. A., and Tsao, D. Y. (2010). Functional compartmentalization and viewpoint generalization within the macaque face-processing system. *Science*, **330**, 845–851.

Gauthier, I., Skudlarski, P., Gore, J. C., and Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience*, **3**, 191–197.

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., and Gore, J. C. (1999). Activation of the middle fusiform “face area” increases with expertise in recognizing novel objects. *Nature Neuroscience*, **2**, 568–573.

Glezer, L. S., Kim, J., Rule, J., Jiang, X., and Riesenhuber, M. (2015). Adding words to the brain’s visual dictionary: Novel word learning selectively sharpens orthographic representations in the VWFA. *Journal of Neuroscience*, **35**, 4965–4972.

Grill-Spector, K., Knouf, N., and Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. *Nature Neuroscience*, **7**, 555–562.

Grill-Spector, K., Sayres, R., and Ress, D. (2006). High-resolution imaging reveals highly selective nonface clusters in the fusiform face area. *Nature Neuroscience*, **9**, 1177–1185.

Grill-Spector, K., and Weiner, K. S. (2014). The functional architecture of the ventral temporal cortex and its role in categorization. *Nature Reviews Neuroscience*, **15**, 536–548.

Gross, C. G. (2005). Processing the facial image: A brief history. *American Psychologist*, **60**, 755–763.

Gross, C. G. (2008). Single neuron studies of inferior temporal cortex. *Neuropsychologia*, **46**, 841–852.

Gross, C. G., Bender, D. B., and Rocha-Miranda, C. E. (1969). Visual receptive fields of neurons in inferotemporal cortex of the monkey. *Science*, **166**, 1303–1306.

Gross, C. G., Rocha-Miranda, C. E., and Bender, D. B. (1972). Visual properties of neurons in inferotemporal cortex of the macaque. *Journal of Neurophysiology*, **35**, 96–111.

Gschwind, M., Pourtois, G., Schwartz, S., van de Ville, D., and Vuilleumier, P. (2012). White-matter connectivity between face-responsive regions in the human brain. *Cerebral Cortex*, **22**, 1564–1576.

Haxby, J. V., Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., and Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, **293**, 2425–2430.

Hayward, W. G., and Tarr, M. J. (1997). Testing conditions for viewpoint invariance in object recognition. *Journal of Experimental Psychology: Human Perception and Performance*, **23**, 1511–1521.

Hoffman, E., and Haxby, J. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience*, **3**, 80–84.

Humphreys, G. and Riddoch, J. (2014). *A case study in visual agnosia revisited: To see but not to see* (2nd edn.). New York: Psychology Press.

Humphreys, G. W., and Forde, E. M. E. (2001). Hierarchies, similarity, and interactivity in object recognition: “Category-specific” neuropsychological deficits. *Behavioral and Brain Sciences*, **24**, 453–509.

Hung, C. P., Kreiman, G., Poggio, T., and DiCarlo, J. J. (2005). Fast readout of object identity from macaque inferior temporal cortex. *Science*, **310**, 863–866.

Jansari, A., Miller, S., Pearce, L., Cobb, S., Sagiv, N., Williams, A. L., Hanley, J. R., et al. (2015). The man who mistook his neuropsychologist for a popstar: When configural processing fails in acquired prosopagnosia. *Frontiers in Human Neuroscience*, **9**, 1–16.

Kaiser, D., Strnad, L., Seidl, K. N., Kastner, S., and Peelen, M. V. (2014). Whole person-evoked fMRI activity patterns in human fusiform gyrus are accurately modeled by a linear combination of face- and body-evoked activity patterns. *Journal of Neurophysiology*, **111**, 82–90.

Kanwisher, N. (2000). Domain specificity in face perception. *Nature Neuroscience*, **3**, 759–763.

Kanwisher, N., and Dilks, D. D. (2014). The functional organization of the ventral visual pathway in humans. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Kanwisher, N., McDermott, J., and Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, **17**, 4302–4311.

Kanwisher, N., and Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society of London*, **361**, 2109–2128.

Kosslyn, S. M., Alpert, N. M., Thompson, W. L., Maljkovic, V., Weise, S. B., Chabris, C. F., Hamilton, S. E., Rauch, S. L., and Buonanno, F. S. (1993). Visual mental imagery activates topographically organized visual cortex: PET investigations. *Journal of Cognitive Neuroscience*, **5**, 263–287.

Kosslyn, S. M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J. P., Thompson, W. L., Ganis, G., Sukel, K. E., and Alpert, N. M. (1999). The role of Area 17 in visual imagery: Convergent evidence from PET and rTMS. *Science*, **284**(5411), 167–170.

Kosslyn, S. M., Thompson, W. L., and Alpert, N. M. (1997). Neural systems shared by visual imagery and visual perception: A positron emission tomography study.

NeuroImage, **6**(4), 320–334.

Kreiman, G., Hung, C. P., Kraskov, A., Quiroga, R. Q., Poggio, T., and DiCarlo, J. J. (2006). Object selectivity of local field potentials and spikes in the macaque inferior temporal cortex. *Neuron*, **49**, 433–445.

Krekelberg, B., Boynton, G. M., and van Wezel, R. J. A. (2006). Adaptation: From single cells to BOLD signals. *Trends in Neurosciences*, **29**, 250–256.

Kriegeskorte, N., Mur, M., Ruff, D. A., Kiani, R., Bodurka, J., Esteky, H., et al. (2008). Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron*, **60**, 1126–1141.

Lee, Y., Duchaine, B., Wilson, H. R., and Nakayama, K. (2010). Three cases of developmental prosopagnosia from one family: Detailed neuropsychological and psychophysical investigation of face processing. *Cortex*, **46**, 949–964.

Lehky, S. R., and Tanaka, K. (2016). Neural representation for object recognition in inferotemporal cortex. *Current Opinion in Neurobiology*, **37**, 23–35.

Lewis, J. W., Brefczynski, R. E., Phinney, R. E., Janik, J. J., and DeYoe, E. A. (2005). Distinct cortical pathways for processing tool versus animal sounds. *Journal of Neuroscience*, **25**, 5148–5158.

Lewis, J. W., Wightman, F. L., Brefczynski, R. E., Phinney, R. E., Binder, J. R., and DeYoe, E. A. (2004). Human brain regions involved in recognizing environmental sounds. *Cerebral Cortex*, **14**, 1008–1021.

Liu, J., Harris, A., and Kanwisher, N. (2010). Perception of face parts and face configurations: An fMRI study. *Journal of Cognitive Neuroscience*, **22**, 203–211.

Logothetis, N. K., and Pauls, J. (1995). Psychophysical and physiological evidence for viewer-centered object representations in the primate. *Cerebral Cortex*, **3**, 270–288.

Lohse, M., Garrido, L., Driver, J., Dolan, R. J., Duchaine, B. C., and Furl, N. (2016). Effective connectivity from early visual cortex to posterior occipitotemporal face areas supports face selectivity and predicts developmental prosopagnosia. *Journal of Neuroscience*, **36**, 3821–3828.

Marr, D. (1982). *Vision*. San Francisco: Freeman.

Martinaud, O., Pouliquen, D., Gérardin, E., Loubeyre, M., Hirsbein, D., Hannequin, D., and Cohen, L. (2012). Visual agnosia and posterior cerebral artery infarcts: An anatomical-clinical study. *PloS ONE*, **7**, e30433.

McKone, E., Kanwisher, N., and Duchaine, B. C. (2006). Can generic expertise explain special processing for faces? *Trends in Cognitive Sciences*, **11**, 8–15.

McNeil, J. E., and Warrington, E. K. (1993). Prosopagnosia: A face-specific disorder. *Quarterly Journal of Experimental Psychology*, **46A**, 1–10.

Moerel, M., de Martino, F., and Formisano, E. (2012). Processing of natural sounds in human auditory cortex: Tonotopy, spectral tuning, and relation to voice sensitivity. *Journal of Neuroscience*, **32**, 14205–14216.

Moscovitch, M., Winocur, G., and Behrmann, M. (1997). What is special about face recognition? Nineteen experiments on a person with visual object agnosia and dyslexia but normal face recognition. *Journal of Cognitive Neuroscience*, **9**, 555–604.

Murty, N. A. R., and Arun, S. P. (2015). Dynamics of 3D view invariance in monkey inferotemporal cortex. *Journal of Neurophysiology*, **113**, 2180–2194.

Nestor, A., Plaut, D. C., and Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences*, **108**, 9998–10003.

Neuner, F., and Schweinberger, S. R. (2000). Neuropsychological impairments in the

recognition of faces, voices, and personal names. *Brain and Cognition*, **44**, 342–366.

Nishimura, M., Scherf, K. S., Zachariou, V., Tarr, M. J., and Behrmann, M. (2015). Size precedes view: Developmental emergence of invariant object representations in lateral occipital complex. *Journal of Cognitive Neuroscience*, **27**, 474–491.

Op de Beeck, H., and Vogels, R. (2000). Spatial sensitivity of macaque inferior temporal neurons. *Journal of Comparative Neurology*, **426**, 505–518.

Pearson, J., and Kosslyn, S. M. (2015). The heterogeneity of mental representation: Ending the imagery debate. *Proceedings of the National Academy of Sciences*, **112**, 10089–10092.

Peelen, M. V., and Downing, P. E. (2007). The neural basis of visual body perception. *Nature Reviews Neuroscience*, **8**, 636–648.

Peissig, J. J., and Tarr, M. J. (2007). Visual object recognition: Do we know more now than we did 20 years ago? *Annual Review of Psychology*, **58**, 75–96.

Perrett, D. I., and Mistlin, A. J. (1990). Perception of facial attributes. In W. C. Stebbins and M. A. Berkley (eds.), *Comparative perception, complex signals*, Vol. II (pp. 187–215). New York: Wiley.

Perrett, D. I., Smith, P. A. J., Potter, D. D., Mistlin, A. J., Head, A. S., Milner, A. D., and Jeeves, M. A. (1985). Visual cells in the temporal cortex sensitive to face view and gaze direction. *Proceedings of the Royal Society of London, Series B*, **223**, 293–317.

Perrodin, C., Kayser, C., Logothetis, N. K., and Petkov, C. I. (2011). Voice cells in the primate temporal lobe. *Current Biology*, **21**, 1408–1415.

Petkov, C. I., Kayser, C., Steudel, T., Whittingstall, K., Augath, M., and Logothetis, N. K. (2008). A voice region in the monkey brain. *Nature Neuroscience*, **11**, 367–374.

-
- Pinsk, M. A., DeSimone, K., Moore, T., Gross, C. G., and Kastner, S. (2005). Representations of faces and body parts in macaque temporal cortex: A functional MRI study. *Proceedings of the National Academy of Sciences*, **102**, 6996–7001.
-
- Pitcher, D., Dilks, D. D., Saxe, R. R., Triantafyllou, C., and Kanwisher, N. (2011). Differential selectivity for dynamic versus static information in face-selective cortical regions. *Neuroimage*, **56**, 2356–2363.
-
- Poggio, T., and Ullman, S. (2013). Vision: Are models of object recognition catching up with the brain? *Annals of the New York Academy of Sciences*, **1305**, 72–82.
-
- Pourtois, G., Peelen, M. V., Spinelli, L., Seeck, M., and Vuilleumier, P. (2007). Direct intracranial recording of body-selective responses in human extrastriate cortex. *Neuropsychologia*, **45**, 262–265.
-
- Prather, S. C., Votaw, J. R., and Sathian, K. (2004). Task-specific recruitment of dorsal and ventral visual areas during tactile perception. *Neuropsychologia*, **42**, 1079–1087.
-
- Pylyshyn, Z. W. (1973). What the mind's eye tells the mind's brain: A critique of mental imagery. *Psychological Bulletin*, **80**, 1–24.
-
- Pylyshyn, Z. W. (1981). The imagery debate: Analogue media versus tacit knowledge. *Psychological Review*, **87**, 16–45.
-
- Quiroga, R. Q. (2012). Concept cells: The building blocks of declarative memory functions. *Nature Reviews Neuroscience*, **13**, 587–597.
-
- Quiroga, R. Q., Reddy, L., Kreiman, G., Koch, C., and Fried, I. (2005). Invariant visual representation by single neurons in the human brain. *Nature*, **435**, 1102–1107.
-
- Ratcliff, G., and Newcombe, F. (1982). Object recognition: Some deductions from the clinical evidence. In A. W. Ellis (ed.), *Normality and pathology in cognitive functions*

(pp. 147–171). London: Academic Press.

Reddy, L., and Kanwisher, N. (2006). Coding of visual objects in the ventral stream. *Current Opinion in Neurobiology*, **16**, 408–414.

Reed, C. L., Caselli, R. J., and Farah, M. J. (1996). Tactile agnosia: Underlying impairment and implications for normal tactile recognition. *Brain*, **199**, 875–888.

Reed, C. L., Klatzky, R. L., and Halgren, E. (2005). What vs. where in touch: An fMRI study. *Neuroimage*, **25**, 718–726.

Reed, C. L., Shoham, S., and Halgren, E. (2004). Neural substrates of tactile object recognition: An fMRI study. *Human Brain Mapping*, **21**, 236–246.

Reed, C. L., Stone, V. E., Bozova, S., and Tanaka, J. (2003). The body-inversion effect. *Psychological Science*, **14**, 302–308.

Reed, C. L., Stone, V. E., Grubb, J. D., and McGoldrick, J. E. (2006). Turning configural processing upside down: Part and whole body postures. *Journal of Experimental Psychology: Human Perception and Performance*, **32**, 73–87.

Rey, H. G., Ison, M. J., Pedreira, C., Valentin, A., Alarcon, G., Selway, R., Quian Quiroga, R., et al. (2015). Single-cell recordings in the human medial temporal lobe. *Journal of Anatomy*, **227**, 394–408.

Rezlescu, C., Barton, J. J., Pitcher, D., and Duchaine, B. (2014). Normal acquisition of expertise with greebles in two cases of acquired prosopagnosia. *Proceedings of the National Academy of Sciences*, **111**, 5123–5128.

Rhodes, G., and Calder, A. J. (2014). Face perception. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Rhodes, G., Tan, S., Brake, S., and Taylor, K. (1989). Expertise and configural coding

in face recognition. *British Journal of Psychology*, **80**, 313–331.

Riesenhuber, M., and Poggio, T. (2000). Models of object recognition. *Nature Neuroscience*, **3**(Suppl.), 1199–1204.

Robbins, R., and McKone, E. (2007). No face-like processing for objects-of-expertise in three behavioural tasks. *Cognition*, **103**, 34–79.

Robertson, L. C., Lamb, M. R., and Knight, R. T. (1988). Effects of lesions of temporal-parietal junction on perceptual and attentional processing in humans. *Journal of Neuroscience*, **8**, 3757–3769.

Rolls, E. T. (2004). Invariant object and face recognition. In L. M. Chalupa and J. S. Werner (eds.), *The visual neurosciences* (pp. 1165–1178). Cambridge, MA: MIT Press.

Rossion, B., and Jacques, C. (2012). The N170: Understanding the time course of face perception in the human brain. In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potential components*. New York: Oxford.

Sato, T., Uchida, G., Lescroart, M. D., Kitazono, J., Okada, M., and Tanifuji, M. (2013). Object representation in inferior temporal cortex is organized hierarchically in a mosaic-like structure. *Journal of Neuroscience*, **33**, 16642–16656.

Schwarzlose, R. F., Baker, C. I., and Kanwisher, N. (2005). Separate face and body selectivity on the fusiform gyrus. *Journal of Neuroscience*, **25**, 11055–11059.

Sergent, J., Ohta, S., and MacDonald, B. (1992). Functional neuroanatomy of face and object processing. *Brain*, **115**, 15–36.

Sergent, J., and Signoret, J.-L. (1992). Varieties of functional deficits in prosopagnosia. *Cerebral Cortex*, **2**, 375–388.

Slevc, L. R., and Shell, A. R. (2015). Auditory agnosia. *Handbook of Clinical*

Neurology, **129**, 573–587.

Slotnick, S. D., Thompson, W. L., and Kosslyn, S. M. (2005). Visual mental imagery induces retinotopically organized activation of early visual areas. *Cerebral Cortex*, **15**, 1570–1583.

Snow, J. C., Goodale, M. A., and Culham, J. C. (2015). Preserved haptic shape processing after bilateral LOC lesions. *Journal of Neuroscience*, **35**, 13745–13760.

Stokes, M., Thompson, R., Cusack, R., and Duncan, J. (2009). Top-down activation of shape-specific population codes in visual cortex during mental imagery. *Journal of Neuroscience*, **29**, 1565–1572.

Susilo, T., and Duchaine, B. (2013). Advances in developmental prosopagnosia research. *Current Opinion in Neurobiology*, **23**, 423–429.

Tamura, H., Kaneko, H., and Fujita, I. (2005). Quantitative analysis of functional clustering of neurons in the macaque inferior temporal cortex. *Neuroscience Research*, **52**, 311–322.

Tarr, M. J., and Bülthoff, H. H. (1998). Image-based object recognition in man, monkey, and machine. *Cognition*, **67**, 1–20.

Tarr, M. J., and Gauthier, I. (2000). FFA: A flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nature Neuroscience*, **3**(8), 764–769.

Thompson, P. (1980). Margaret Thatcher: A new illusion. *Perception*, **9**, 483–484.

Thompson-Schill, S. L., Aguirre, G. K., D'Esposito, M., and Farah, M. J. (1999). A neural basis of category and modality specificity of semantic knowledge. *Neuropsychologia*, **37**, 671–676.

Towler, J., and Eimer, M. (2012). Electrophysiological studies of face processing in

developmental prosopagnosia: Neuropsychological and neurodevelopmental perspectives. *Cognitive Neuropsychology*, **29**, 503–529.

Tsao, D. Y., Freiwald, W. A., Knutsen, T. A., Mandeville, J. B., and Tootell, R. B. H. (2003). Faces and objects in macaque cerebral cortex. *Nature Neuroscience*, **6**, 989–995.

Tsao, D. Y., Freiwald, W. A., Tootell, R. B. H., and Livingstone, M. S. (2006). A cortical region consisting entirely of face-selective cells. *Science*, **311**, 670–674.

Urgesi, C., Candidi, M., Ionta, S., and Aglioti, S. M. (2007). Representation of body identity and body actions in extrastriate body area and ventral premotor cortex. *Nature Neuroscience*, **10**, 30–31.

von Kriegstein, K., Kleinschmidt, A., Sterzer, P., and Giraud, A.-L. (2005). Interaction of face and voice areas during speaker recognition. *Journal of Cognitive Neuroscience*, **17**, 367–376.

Warrington, E. K. (1975). The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, **27**, 187–199.

Warrington, E. K., and Shallice, T. (1984). Category specific semantic impairments. *Brain*, **107**, 829–854.

Weiner, K. S., and Grill-Spector, K. (2011). Not one extrastriate body area: Using anatomical landmarks, hMT+, and visual field maps to parcellate limb-selective activations in human lateral occipitotemporal cortex. *Neuroimage*, **56**, 2183–2199.

Weiner, K. S., and Grill-Spector, K. (2013). Neural representations of faces and limbs neighbor in human high-level visual cortex: Evidence for a new organization principle. *Psychological Research*, **77**, 74–97.

Weiss, N., Mardo, E., and Avidan, G. (2016). Visual expertise for horses in a case of

congenital prosopagnosia. *Neuropsychologia*, **83**, 63–75.

Wilson, H. R., and Wilkinson, F. (2015). From orientations to objects: Configural processing in the ventral stream. *Journal of Vision*, **15**, 1–10.

Yamane, Y., Tsunoda, K., Matsumoto, M., Phillips, A. N., and Tanifuji, M. (2006). Representation of the spatial relationship among object parts by neurons in macaque inferotemporal cortex. *Journal of Neurophysiology*, **96**, 3147–3156.

Yasuda, M., Banno, T., and Komatsu, H. (2010). Color selectivity of neurons in the posterior inferior temporal cortex of the macaque monkey. *Cerebral Cortex*, **20**, 1630–1646.

Yin, R. K. (1970). Face recognition by brain-injured patients: A dissociable ability? *Neuropsychologia*, **8**, 395–402.

Yoshor, D., Bosking, W. H., Ghose, G. M., and Maunsell, J. H. R. (2007). Receptive fields in human visual cortex mapped with surface electrodes. *Cerebral Cortex*, **17**, 2293–2302.

Yovel, G., and Belin, P. (2013). A unified coding strategy for processing faces and voices. *Trends in Cognitive Sciences*, **17**, 263–271.

Yovel, G., and Kanwisher, N. (2004). Face perception: Domain specific, not process specific. *Neuron*, **44**, 889–898.

Zangenehpour, S., and Chaudhuri, A. (2005). Patchy organization and asymmetric distribution of the neural correlates of face processing in monkey inferotemporal cortex. *Current Biology*, **15**, 993–1005.

Zvyagintsev, M., Clemens, B., Chechko, N., Mathiak, K. A., Sack, A. T., and Mathiak, K. (2013). Brain networks underlying mental imagery of auditory and visual information. *European Journal of Neuroscience*, **37**, 1421–1434.

Chapter 7

Aguirre, G. K. (2003). Topographical disorientation: A disorder of way-finding ability. In M. D'Esposito (ed.), *Neurological foundations of cognitive neuroscience* (pp. 89–108). Cambridge, MA: MIT Press.

Alexander, A. S., and Nitz, D. A. (2015). Retrosplenial cortex maps the conjunction of internal and external spaces. *Nature Neuroscience*, **18**, 1143–1151.

Amalric, M., and Dehaene, S. (2016). Origins of the brain networks for advanced mathematics in expert mathematicians. *Proceedings of the National Academy of Sciences*, **113**, 4909–4917.

Andersen, R. A., Andersen, K. N., Hwang, E. J., and Hauschild, M. (2014). Optic ataxia: From Balint's syndrome to the parietal reach region. *Neuron*, **81**, 967–983.

Andersen, R. A., and Mountcastle, V. B. (1983). The influence of the angle of gaze upon the excitability of the light-sensitive neurons of the posterior parietal cortex. *Journal of Neuroscience*, **3**, 532–548.

Astafiev, S. V., Shulman, G. L., Stanley, C. M., Snyder, A. Z., van Essen, D. C., and Corbetta, M. (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *Journal of Neuroscience*, **23**, 4689–4699.

Avillac, M., Deneve, S., Olivier, E., Pouget, A., and Duhamel, J.-R. (2005). Reference frames for representing visual and tactile locations in parietal cortex. *Nature Neuroscience*, **8**, 941–949.

Balslev, D., and Miall, R. C. (2008). Eye position representation in human anterior parietal cortex. *Journal of Neuroscience*, **28**, 8968–8972.

Batista, A. P., Buneo, C. A., Snyder, L. H., and Andersen, R. A. (1999). Reach plans in eye-centered coordinates. *Science*, **285**, 257–260.

Battaglia-Mayer, A., and Caminiti, R. (2002). Optic ataxia as a result of the breakdown of the global tuning fields of parietal neurones. *Brain*, **125**, 225–237.

Battaglia-Mayer, A., Ferrari-Toniolo, S., Visco-Comandini, F., Archambault, P. S., Saberi-Moghadam, S., and Caminiti, R. (2013). Impairment of online control of hand and eye movements in a monkey model of optic ataxia. *Cerebral Cortex*, **23**, 2644–2656.

Becker, H. G., Haarmeier, T., Tatagiba, M., and Gharabaghi, A. (2013). Electrical stimulation of the human homolog of the medial superior temporal area induces visual motion blindness. *Journal of Neuroscience*, **33**, 18288–18297.

Benton, A. L. (1967). Constructional apraxia and the minor hemisphere. *Confinia Neurologica*, **29**, 1–16.

Biesbroek, J. M., van Zandvoort, M. J., Kuijf, H. J., Weaver, N. A., Kappelle, L. J., Vos, P. C., and Utrecht VCI Study Group. (2014). The anatomy of visuospatial construction revealed by lesion-symptom mapping. *Neuropsychologia*, **62**, 68–76.

Born, R. T., and Bradley, D. C. (2005). Structure and function of visual area MT. *Annual Review of Neuroscience*, **28**, 157–189.

Bosco, G., Carrozzo, M., and Lacquaniti, F. (2008). Contributions of the human temporoparietal junction and MT/V5+ to the timing of interception revealed by transcranial magnetic stimulation. *Journal of Neuroscience*, **28**, 12071–12804.

Bremmer, F., Kubischik, M., Pekel, M., Hoffmann, K. P., and Lappe, M. (2010). Visual selectivity for heading in monkey area MST. *Experimental Brain Research*, **200**, 51–60.

Breveglieri, R., Hadjidimitrakis, K., Bosco, A., Sabatini, S. P., Galletti, C., and Fattori, P. (2012). Eye position encoding in three-dimensional space: Integration of version and vergence signals in the medial posterior parietal cortex. *Journal of Neuroscience*, **32**,

159–169.

Bridge, H., Clare, S., and Krug, K. (2014). Delineating extrastriate visual area MT (V5) using cortical myeloarchitecture. *NeuroImage*, **93**, 231–236.

Britten, K. H., and van Wezel, R. J. (1998). Electrical microstimulation of cortical area MST biases heading perception in monkeys. *Nature Neuroscience*, **1**, 59–63.

Chechlacz, M., Novick, A., Rotshtein, P., Bickerton, W. L., Humphreys, G. W., and Demeyere, N. (2014). The neural substrates of drawing: A voxel-based morphometry analysis of constructional, hierarchical, and spatial representation deficits. *Journal of Cognitive Neuroscience*, **26**, 2701–2715.

Chen, A., DeAngelis, G. C., and Angelaki, D. E. (2011). Representation of vestibular and visual cues to self-motion in ventral intraparietal cortex. *Journal of Neuroscience*, **31**, 12036–12052.

Chen, A., Gu, Y., Liu, S., DeAngelis, G. C., and Angelaki, D. E. (2016). Evidence for a causal contribution of macaque vestibular, but not intraparietal, cortex to heading perception. *Journal of Neuroscience*, **36**, 3789–3798.

Committeri, G., Pitzalis, S., Galati, G., Patria, F., Pelle, G., Sabatini, U., Pizzamiglio, L., et al. (2007). Neural bases of personal and extrapersonal neglect in humans. *Brain*, **130**, 431–441.

Corbetta, M., and Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, **34**, 569–599.

Crowe, D. A., Averbeck, B. B., and Chafee, M. V. (2008). Neural ensemble coding reveals a correlate of viewer- to object-centered spatial transformation in monkey parietal cortex. *Journal of Neuroscience*, **28**, 5218–5228.

Czuba, T. B., Huk, A. C., Cormack, L. K., and Kohn, A. (2014). Area MT encodes

three-dimensional motion. *Journal of Neuroscience*, **34**, 15522–15533.

DeAngelis, G. C., Cumming, B. G., and Newsome, W. T. (1998). Cortical area MT and the perception of stereoscopic depth. *Nature*, **394**, 677–680.

de Haan, E. H., and Cowey, A. (2011). On the usefulness of “what” and “where” pathways in vision. *Trends in Cognitive Sciences*, **15**, 460–466.

Della-Maggiore, V., Malfait, N., Ostry, D. J., and Paus, T. (2004). Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. *Journal of Neuroscience*, **24**, 9971–9976.

di Pellegrino, G., and Làdavas, E. (2015). Peripersonal space in the brain. *Neuropsychologia*, **66**, 126–133.

Duffy, C.J. (2014). The cortical analysis of optic flow: Mechanism, function, and dysfunction. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., and Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature*, **425**, 184–187.

Epstein, R., DeYoe, E. A., Press, D. Z., Rosen, A. C., and Kanwisher, N. (2001). Neuropsychological evidence for a topographical learning mechanism in parahippocampal cortex. *Cognitive Neuropsychology*, **18**, 481–508.

Epstein, R. A., Parker, W. E., and Feiler, A. M. (2007). Where am I now? Distinct roles for parahippocampal and retrosplenial cortices in place recognition. *Journal of Neuroscience*, **27**, 6141–6149.

Epstein, R. A., and Vass, L. K. (2014). Neural systems for landmark-based wayfinding in humans. *Philosophical Transactions of the Royal Society of London, Series B*, **369**,

20120533.

Fattori, P., Breveglieri, R., Bosco, A., Gamberini, M., and Galletti, C. (2017). Vision for prehension in the medial parietal cortex. *Cerebral Cortex*, **27**, 1149–1163.

Franciotti, R., D'Ascenzo, S., Di Domenico, A., Onofrij, M., Tommasi, L., and Laeng, B. (2013). Focusing narrowly or broadly attention when judging categorical and coordinate spatial relations: a MEG study. *PloS ONE*, **8**, e83434.

Frey, S. H., Vinton, D., Norlund, R., and Grafton, S. T. (2005). Cortical topography of human anterior intraparietal cortex active during visually guided grasping. *Cognitive Brain Research*, **23**, 397–405.

Glover, S., Miall, R. C., and Rushworth, M. F. S. (2005). Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size. *Journal of Cognitive Neuroscience*, **17**, 124–136.

Goodale, M. A. (2014). Visuomotor control. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Gu, Y., DeAngelis, G. C., and Angelaki, D. E. (2007). A functional link between area MSTd and heading perception based on vestibular signals. *Nature Neuroscience*, **10**, 1038–1047.

Gu, Y., DeAngelis, G. C., and Angelaki, D. E. (2012). Causal links between dorsal medial superior temporal area neurons and multisensory heading perception. *Journal of Neuroscience*, **32**, 2299–2313.

Haarmeier, T., Thier, P., Repnow, M., and Petersen, D. (1997). False perception of motion in a patient who cannot compensate for eye movements. *Nature*, **389**, 849–852.

Hadjidimitrakis, K., Bertozzi, F., Breveglieri, R., Bosco, A., Galletti, C., and Fattori, P. (2014). Common neural substrate for processing depth and direction signals for

reaching in the monkey medial posterior parietal cortex. *Cerebral Cortex*, **24**, 1645–1657.

Haijima, A., and Ichitani, Y. (2008). Anterograde and retrograde amnesia of place discrimination in retrosplenial cortex and hippocampal lesioned rats. *Learning and Memory*, **15**, 477–482.

Halberda, J., Mazocco, M. M., and Feigenson, L. (2008). Individual differences in non-verbal number acuity correlate with maths achievement. *Nature*, **455**, 665–668.

Halligan, P. W., Fink, G. R., Marshall, J. C., and Vallar, G. (2003). Spatial cognition: Evidence from visual neglect. *Trends in Cognitive Sciences*, **7**, 125–133.

Hannagan, T., Amedi, A., Cohen, L., Dehaene-Lambertz, G., and Dehaene, S. (2015). Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. *Trends in Cognitive Sciences*, **19**, 374–382.

Harris, L. J., and Gitterman, S. R. (1978). University professors' self-descriptions of left-right confusability: Sex and handedness differences. *Perceptual and Motor Skills*, **47**, 819–823.

Hartley, T., Lever, C., Burgess, N., and O'Keefe, J. (2014). Space in the brain: How the hippocampal formation supports spatial cognition. *Philosophical Transactions of the Royal Society of London, Series B*, **369**, 20120510.

Harvey, B. M., Klein, B. P., Petridou, N., and Dumoulin, S. O. (2013). Topographic representation of numerosity in the human parietal cortex. *Science*, **341**, 1123–1126.

Hashimoto, R., Tanaka, Y., and Nakano, I. (2010). Heading disorientation: A new test and a possible underlying mechanism. *European Neurology*, **63**, 87–93.

Hesselmann, G., Kell, C. A., and Kleinschmidt, A. (2008). Ongoing activity fluctuations in hMT+ bias the perception of coherent visual motion. *Journal of Neuroscience*, **28**,

14481–14485.

Holmes, G., and Horax, G. (1919). Disturbances of spatial orientation and visual attention, with loss of stereoscopic vision. *Archives of Neurology and Psychiatry*, **1**, 385–407.

Husain, M., and Nachev, P. (2007). Space and the parietal cortex. *Trends in Cognitive Sciences*, **11**, 30–36.

Hwang, E. J., Hauschild, M., Wilke, M., and Andersen, R. A. (2012). Inactivation of the parietal reach region causes optic ataxia, impairing reaches but not saccades. *Neuron*, **76**, 1021–1029.

Hwang, E. J., Hauschild, M., Wilke, M., and Andersen, R. A. (2014). Spatial and temporal eye–hand coordination relies on the Parietal Reach Region. *Journal of Neuroscience*, **34**, 12884–12892.

Izard, V., Dehaene-Lambertz, G., and Dehaene, S. (2008). Distinct cerebral pathways for object identity and number in human infants. *PLoS Biology*, **6**, e11.

Jackson, S. R., Newport, R., Husain, M., Fowlie, J. E., O'Donoghue, M., and Bajaj, N. (2009). There may be more to reaching than meets the eye: Re-thinking optic ataxia. *Neuropsychologia*, **47**, 1397–1408.

Jacobs, J., Weidemann, C. T., Miller, J. F., Solway, A., Burke, J. F., Wei, X. X., Kahana, M. J., et al. (2013). Direct recordings of grid-like neuronal activity in human spatial navigation. *Nature Neuroscience*, **16**, 1188–1190.

Jakobson, L. S., Archibald, Y. M., Carey, D. P., and Goodale, M. A. (1991). A kinematic analysis of reaching and grasping movements in a patient recovering from optic ataxia. *Neuropsychologia*, **29**, 803–809.

James, T. W., Culham, J., Humphrey, G. K., Milner, A. D., and Goodale, M. A. (2003).

Ventral occipital lesions impair object recognition but not object-directed grasping: An fMRI study. *Brain*, **126**, 2463–2475.

Janssen, P., Srivastava, S., Ombelet, S., and Orban, G. A. (2008). Coding of shape and position in macaque lateral intraparietal area. *Journal of Neuroscience*, **28**, 6679–6690.

Janzen, G., and van Turenout, M. (2004). Selective neural representations of objects relevant for navigation. *Nature Neuroscience*, **7**, 673–677.

Khawaja, F. A., Liu, L. D., and Pack, C. C. (2013). Responses of MST neurons to plaid stimuli. *Journal of Neurophysiology*, **110**, 63–74.

Kosslyn, S. M. (2006). You can play 20 questions with nature and win: Categorical versus coordinate spatial relations as a case study. *Neuropsychologia*, **44**, 1519–1523.

Kravitz, D. J., Saleem, K. S., Baker, C. I., and Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews Neuroscience*, **12**, 217–230.

Large, I., Bridge, H., Ahmed, B., Clare, S., Kolasinski, J., Lam, W., Daubney, G., et al. (2016). Individual differences in the alignment of structural and functional markers of the V5/MT complex in primates. *Cerebral Cortex*, e-publication in advance of print.

Lezak, M. D. (1983). *Neuropsychology Assessment* (2nd edn.). Oxford: Oxford University Press.

Liu, J., and Newsome, W. T. (2005). Correlation between speed perception and neural activity in the middle temporal visual area. *Journal of Neuroscience*, **25**, 711–722.

Maguire, E. A., Frackowiak, R. S., and Frith, C. D. (1997). Recalling routes around London: Activation of the right hippocampus in taxi drivers. *Journal of Neuroscience*, **17**, 7103–7110.

Makuuchi, M., Kaminaga, T., and Sugishita, M. (2003). Both parietal lobes are involved

in drawing: A functional MRI study and implications for constructional apraxia. *Cognitive Brain Research*, **16**, 338–347.

Marchette, S. A., Vass, L. K., Ryan, J., and Epstein, R. A. (2015). Outside looking in: Landmark generalization in the human navigational system. *Journal of Neuroscience*, **35**, 14896–14908.

Martinaud, O., Mirlink, N., Bioux, S., Bliiaux, E., Lebas, A., Gerardin, E., and Hannequin, D. (2014). Agnosia for mirror stimuli: A new case report with a small parietal lesion. *Archives of Clinical Neuropsychology*, **29**, 724–728.

McCloskey, M., Rapp, B., Yantis, S., Rubin, G., Bacon, W. F., Dagnelie, G., et al. (1995). A developmental deficit in localizing objects from vision. *Psychological Science*, **6**, 112–117.

Medina, J., Kannan, V., Pawlak, M., Kleinman, J. T., Newhart, M., Davis, C., et al. (2009). Neural substrates of visuospatial processing in distinct reference frames: Evidence from unilateral spatial neglect. *Journal of Cognitive Neuroscience*, **21**, 2073–2084.

Milner, A. D., Dijkerman, H. C., McIntosh, R. D., Rossetti, Y., and Pisella, L. (2003). Delayed reaching and grasping in patients with optic ataxia. *Progress in Brain Research*, **142**, 225–242.

Morgan, L. K., MacEvoy, S. P., Aguirre, G. K., and Epstein, R. A. (2011). Distances between real-world locations are represented in the human hippocampus. *Journal of Neuroscience*, **31**, 1238–1245.

Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. *Learning and Motivation*, **12**, 239–260.

Moser, E., Kropff, E., and Moser, M. B. (2008). Place cells, grid cells, and the brain's spatial representation system. *Annual Review of Neuroscience*, **31**, 69–89.

Motter, B. C., and Mountcastle, V. B. (1981). The functional properties of light-sensitive neurons of the posterior parietal cortex studies in waking monkeys: Foveal sparing and opponent vector organization. *Journal of Neuroscience*, **1**, 3–26.

Mullette-Gillman, O. A., Cohen, Y. E., and Groh, J. M. (2005). Eye-centered, head-centered, and complex coding of visual and auditory targets in the intraparietal sulcus. *Journal of Neurophysiology*, **94**, 2331–2352.

Nadler, J. W., Barbash, D., Kim, H. R., Shimpf, S., Angelaki, D. E., and DeAngelis, G. C. (2013). Joint representation of depth from motion parallax and binocular disparity cues in macaque area MT. *Journal of Neuroscience*, **33**, 14061–14074.

Nakamura, K., Chung, H. H., Graziano, M. S. A., and Gross, C. G. (1999). Dynamic representation of eye position in the parieto-occipital sulcus. *Journal of Neurophysiology*, **81**, 2374–2385.

Nichols, M. J., and Newsome, W. T. (2002). Middle temporal visual area microstimulation influences veridical judgments of motion direction. *Journal of Neuroscience*, **22**, 9530–9540.

Nieder, A., and Dehaene, S. (2009). Representation of number in the brain. *Annual Review of Neuroscience*, **32**, 185–208.

Nieder, A., and Miller, E. K. (2004). A parieto-frontal network for visual numerical information in the monkey. *Proceedings of the National Academy of Sciences*, **101**, 7457–7462.

Ogawa, K., and Inui, T. (2009). The role of the posterior parietal cortex in drawing by copying. *Neuropsychologia*, **47**, 1013–1022.

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, **34**(1), 171–175.

Orban, G. A., and Jastorff, J. (2014). Functional mapping of motion regions in human and nonhuman primates. In J. S. Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Parker, A. J., Smith, J. E. T., and Krug, K. (2016). Neural architectures for stereo vision. *Philosophical Transactions of the Royal Society, B*, **371**, 20150261.

Piazza, M., Pinel, P., Le Bihan, D., and Dehaene, S. (2007). A magnitude code common to numerosities and number symbols in human intraparietal cortex. *Neuron*, **53**, 293–305.

Pothuizen, H. H. J., Aggleton, J. P., and Vann, S. D. (2008). Do rats with retrosplenial cortex lesions lack direction? *European Journal of Neuroscience*, **28**, 2486–2498.

Roe, A. W., Parker, A. J., Born, R. T., and DeAngelis, G. C. (2007). Disparity channels in early vision. *Journal of Neuroscience*, **27**, 11820–11831.

Rozzi, S., Ferrari, P. F., Bonini, L., Rizzolatti, G., and Fogassi, L. (2008). Functional organization of inferior parietal lobule convexity in the macaque monkey: Electrophysiological characterization of motor, sensory, and mirror responses and their correlation with cytoarchitectonic areas. *European Journal of Neuroscience*, **28**, 1569–1588.

Rugani, R., Vallortigara, G., Priftis, K., and Regolin, L. (2015). Number-space mapping in the newborn chick resembles humans' mental number line. *Science*, **347**, 534–536.

Rushworth, M. F. S., Paus, T., and Sipila, P. K. (2001). Attention systems and the organization of the human parietal cortex. *Journal of Neuroscience*, **21**, 5262–5271.

Sanada, T. M., and DeAngelis, G. C. (2014). Neural representation of motion-in-depth in area MT. *Journal of Neuroscience*, **34**, 15508–15521.

Schenk, T., Ellison, A., Rice, N., and Milner, A. D. (2005). The role of V5/MT+ in the

control of catching movements: An rTMS study. *Neuropsychologia*, **43**, 189–198.

Schinazi, V. R., Nardi, D., Newcombe, N. S., Shipley, T. F., and Epstein, R. A. (2013). Hippocampal size predicts rapid learning of a cognitive map in humans. *Hippocampus*, **23**, 515–528.

Schindler, I., Rice, N. J., McIntosh, R. D., Rossetti, Y., Vighetto, A., and Milner, A. D. (2004). Automatic avoidance of obstacles is a dorsal stream function: Evidence from optic ataxia. *Nature Neuroscience*, **7**, 779–784.

Semmes, J., Weinstein, S., Ghent, L., and Teuber, H.-L. (1955). Spatial orientation: 1. Analysis of locus of lesion. *Journal of Psychology*, **39**, 227–244.

Seurinck, R., de Lange, F. P., Achten, E., and Vingerhoets, G. (2011). Mental rotation meets the motion aftereffect: The role of hV5/MT+ in visual mental imagery. *Journal of Cognitive Neuroscience*, **23**, 1395–1404.

Sim, E. J., Helbig, H. B., Graf, M., and Kiefer, M. (2015). When action observation facilitates visual perception: Activation in visuo-motor areas contributes to object recognition. *Cerebral Cortex*, **25**, 2907–2918.

Slotnick, S. D., and Moo, L. R. (2006). Prefrontal cortex hemispheric specialization for categorical and coordinate visual spatial memory. *Neuropsychologia*, **44**, 1560–1568.

Snyder, L. H., Batista, A. P., and Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, **386**, 167–170.

Snyder, L. H., Grieve, K. L., Brotchie, P., and Andersen, R. A. (1998). Separate body- and world-reference representations of visual space in parietal cortex. *Nature*, **394**, 887–891.

Sommer, M. A., and Wurtz, R. H. (2014). The dialogue between cerebral cortex and superior colliculus: Multiple ascending pathways for corollary discharge. In J. S.

Werner and L. M. Chalupa (eds.), *The new visual neurosciences*. Cambridge, MA: MIT Press.

Sutherland, R. J., Whishaw, I. Q., and Kolb, B. (1983). A behavioral analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. *Behavioral Brain Research*, **7**, 133–153.

Tootell, R. B. H., Reppas, J. B., Kwong, K. K., Malach, R., Born, R. T., Brady, T. J., Rosen, B. R., and Belliveau, J. W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *Journal of Neuroscience*, **15**, 3215–3230.

Trojano, L., Conson, M., Maffei, R., and Grossi, D. (2006). Categorical and coordinate spatial processing in the imagery domain investigated by rTMS. *Neuropsychologia*, **44**(9), 1569–1574.

Trojano, L., Fragassi, N. A., Chicacchio, L., Izzo, O., Izzo, G., Di Cesare, G., Cristinzio, C., and Grossi, D. (2004). Relationships between constructional and visuospatial abilities in normal subjects and in focal brain-damaged patients. *Journal of Clinical and Experimental Neuropsychology*, **26**, 1103–1112.

Tudusciuc, O., and Nieder, A. (2007). Neuronal population coding of continuous and discrete quantity in the primate posterior parietal cortex. *Proceedings of the National Academy of Sciences*, **104**, 14513–14518.

Tunik, E., Frey, S. H., and Grafton, S. T. (2005). Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. *Nature Neuroscience*, **8**, 505–511.

Uka, T., and DeAngelis, G. C. (2006). Linking neural representation to function in stereoscopic depth perception: Roles of the middle temporal area in coarse versus fine disparity discrimination. *Journal of Neuroscience*, **26**, 6791–6802.

van der Ham, I. J., Duijndam, M. J., Raemaekers, M., van Wezel, R. J., Oleksiak, A., and Postma, A. (2012). Retinotopic mapping of categorical and coordinate spatial relation processing in early visual cortex. *PloS ONE*, **7**, e38644.

van der Ham, I. J., Postma, A., and Laeng, B. (2014). Lateralized perception: The role of attention in spatial relation processing. *Neuroscience and Biobehavioral Reviews*, **45**, 142–148.

van Der Werf, J., Jensen, O., Fries, P., and Medendorp, W. P. (2008). Gamma-band activity in human posterior parietal cortex encodes the motor goal during delayed prosaccades and antisaccades. *Journal of Neuroscience*, **28**, 8397–8405.

van Polanen, V., and Davare, M. (2015). Interactions between dorsal and ventral streams for controlling skilled grasp. *Neuropsychologia*, **79**, 186–191.

Vass, L. K., and Epstein, R. A. (2013). Abstract representations of location and facing direction in the human brain. *Journal of Neuroscience*, **33**, 6133–6142.

Vass, L. K., and Epstein, R. A. (2016). Common neural representations for visually guided reorientation and spatial imagery. *Cerebral Cortex*, e-publication in advance of print.

Verdon, V., Schwartz, S., Lovblad, K. O., Hauert, C. A., and Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and its functional components: A study using voxel-based lesion-symptom mapping. *Brain*, **133**, 880–894.

Vesia, M., and Crawford, J. D. (2012). Specialization of reach function in human posterior parietal cortex. *Experimental Brain Research*, **221**, 1–18.

von Helmholtz, H. (1910/1925). *Treatise on physiological optics*. English translation: Optical Society of America, Dover Publications.

Wang, X., Zhang, M., Cohen, I. S., and Goldberg, M. E. (2007). The proprioceptive

representation of eye position in monkey primary somatosensory cortex. *Nature Neuroscience*, **10**, 640–646.

Whitney, D., Ellison, A., Rice, N. J., Arnold, D., Goodale, M., Walsh, V., and Milner, D. (2007). Visually guided reaching depends on motion area MT+. *Cerebral Cortex*, **17**, 2644–2649.

Woollett, K., and Maguire, E. A. (2011). Acquiring “the Knowledge” of London’s layout drives structural brain changes. *Current Biology*, **21**, 2109–2114.

Zeki, S. (2015). Area V5 – A microcosm of the visual brain. *Frontiers in Integrative Neuroscience*, **9**.

Zeki, S. M. (1974). Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *Journal of Physiology*, **236**, 549–573.

Zhang, M., and Barash, S. (2000). Neuronal switching of sensorimotor transformations for antisaccades. *Nature*, **408**, 971–975.

Zihl, J., von Cramon, D., and Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain*, **106**, 313–340.

Chapter 8

AbdulSabur, N. Y., Xu, Y., Liu, S., Chow, H. M., Baxter, M., Carson, J., and Braun, A. R. (2014). Neural correlates and network connectivity underlying narrative production and comprehension: A combined fMRI and PET study. *Cortex*, **57**, 107–127. <http://doi.org/10.1016/j.cortex.2014.01.017>

Abutalebi, J., Brambati, S. M., Annoni, J. M., Moro, A., Cappa, S. F., and Perani, D. (2007). The neural cost of the auditory perception of language switches: An event-related fMRI study in bilinguals. *Journal of Neuroscience*, **27**, 13762–13769.

Allen, J. S., Emmorey, K., Bruss, J., and Damasio, H. (2008). Morphology of the insula in relation to hearing status and sign language experience. *Journal of Neuroscience*, **28**, 11900–11905.

Alossa, N., and Castelli, L. (2009). Amusia and musical functioning. *European Neurology*, **61**, 269–277.

Baker, E., Blumstein, S. E., and Goodglass, H. (1981). Interaction between phonological and semantic factors in auditory comprehension. *Neuropsychologia*, **19**, 1–16.

Bartolo, A., Benuzzi, F., Nocetti, L., Baraldi, P., and Nichelli, P. (2006). Humor comprehension and appreciation: An FMRI study. *Journal of Cognitive Neuroscience*, **18**, 1789–1798.

Bauer, P. R., Reitsma, J. B., Houweling, B. M., Ferrier, C. H., and Ramsey, N. F. (2014). Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. *Journal of Neurology, Neurosurgery, and Psychiatry*, **85**(5), 581–588. <http://doi.org/10.1136/jnnp-2013-305659>

Baxendale, S. (2009). The Wada test. *Current Opinion in Neurology*, **22**, 185–189.

Beauvois, M.-F., and Derouesne, J. (1981). Lexical or orthographic dysgraphia. *Brain*, **104**, 21–50.

Beeman, M. (1993). Semantic processing in the right hemisphere may contribute to drawing inferences during comprehension. *Brain and Language*, **44**, 80–120.

Behrens, S. (1988). The role of the right hemisphere in the production of linguistic stress. *Brain and Language*, **33**, 104–127.

Belyk, M., and Brown, S. (2014). Perception of affective and linguistic prosody: An ALE meta-analysis of neuroimaging studies. *Social Cognitive and Affective Neuroscience*, **9**(9), 1395–1403.

Benowitz, L. I., Bear, D. M., Rosenthal, R., Mesulam, M.-M., Zaidel, E., and Sperry, R. W. (1983). Hemispheric specialization in nonverbal communication. *Cortex*, **19**, 5–12.

Benson, D. F., and Geschwind, N. (1972). Aphasia and related disturbances. In A. B. Baker (ed.), *Clinical neurology*. New York: Harper & Row.

Benz, S., Sellaro, R., Hommel, B., and Colzato, L. S. (2015). Music makes the world go round: The impact of musical training on non-musical cognitive functions-a review. *Frontiers in Psychology*, **6**, 2023.

Berken, J. A., Gracco, V. L., Chen, J.-K., Soles, J., Watkins, K. E., Baum, S., et al. (2015). Neural activation in speech production and reading aloud in native and non-native languages. *NeuroImage*, **112**, 208–217.

Blumstein, S. (1991). Phonological aspects of aphasia. In M. Sarno (ed.), *Acquired aphasia* (pp. 129–155). New York: Academic Press.

Bolger, D. J., Perfetti, C. A., and Schneider, W. (2005). Cross-cultural effect on the brain revisited: Universal structures plus writing system variation. *Human Brain Mapping*, **25**, 92–104.

Bottini, G., Corcoran, R., Sterzi, R., Paulesu, E., Schenone, P., Scarpa, P., Frackowiak, R. S., and Frith, C. D. (1994). The role of the right hemisphere in the interpretation of figurative aspects of language. A positron emission tomography activation study. *Brain*, **117**, 1241–1253.

Brownell, H. (1988). Appreciation of metaphoric and connotative word meaning by brain-damaged patients. In C. Chiarello (ed.), *Right hemisphere contributions to lexical semantics* (pp. 19–31). New York: Springer-Verlag.

Brownell, H. H., Michel, D., Powelson, J. A., and Gardner, H. (1983). Surprise but not coherence: Sensitivity to verbal humor in right hemisphere patients. *Brain and Language*, **18**, 20–27.

Buetler, K. A., de León Rodríguez, D., Laganaro, M., Müri, R., Spierer, L., and Annoni, J.-M. (2014). Language context modulates reading route: An electrical neuroimaging study. *Frontiers in Human Neuroscience*, **8**, 83.

Burgess, C., and Simpson, G. B. (1988). Cerebral hemispheric mechanisms in the retrieval of ambiguous word meanings. *Brain and Language*, **33**, 86–103.

Burgund, E. D., and Marsolek, C. J. (1997). Letter-case-specific priming in the right cerebral hemisphere with a form-specific perceptual identification task. *Brain and Cognitive Sciences*, **35**, 239–258.

Burton, M. W., Locasto, P. C., Krebs-Noble, D., and Gullapalli, R. P. (2005). A systematic investigation of the functional neuroanatomy of auditory and visual phonological processing. *NeuroImage*, **26**(3), 647–661.

Capek, C. M., Grossi, G., Newman, A. J., McBurney, S. L., Corina, D., Roeder, B., and Neville, H. J. (2009). Brain systems mediating semantic and syntactic processing in deaf native signers: Biological invariance and modality specificity. *Proceedings of the National Academy of Sciences*, **106**, 8784–8789.

Caramazza, A., Berndt, R. S., Basili, A. G., and Koller, J. J. (1981). Syntactic processing deficits in aphasia. *Cortex*, **17**(3), 333–348.

Caramazza, A., and Zurif, E. (1976). Dissociation of algorithmic and heuristic processes in language comprehension. *Brain and Language*, **3**, 572–582.

Carreiras, M., Seghier, M. L., Baquero, S., Estévez, A., Lozano, A., Devlin, J. T., and Price, C. J. (2009). An anatomical signature for literacy. *Nature*, **461**(7266), 983–986.

Catani, M., and Mesulam, M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex*, **44**(8), 953–961.

Chai, X. J., Berken, J. A., Barbeau, E. B., Soles, J., Callahan, M., Chen, J.-K., and Klein, D. (2016). Intrinsic functional connectivity in the adult brain and success in second-language learning. *The Journal of Neuroscience*, **36**(3), 755–761.

Chiarello, C. (1991). Interpretation of word meanings by the cerebral hemispheres: One is not enough. In P. J. Schwanenflugel (ed.), *The psychology of word meanings* (pp.251–278). Hillsdale, NJ: Erlbaum.

Chou, T. L., Booth, J. R., Burman, D. D., Bitan, T., Bigio, J. D., Lu, D., and Cone, N. E. (2006). Developmental changes in the neural correlates of semantic processing. *NeuroImage*, **29**, 1141–1149.

Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M.-A., and Michel, F. (2000). The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-

brain patients. *Brain*, **123**, 291–307.

Coltheart, M. (1982). The psycholinguistic analysis of acquired dyslexias: Some illustrations. *Philosophical Transactions of the Royal Society of London, Series B*, **298**, 151–164.

Coltheart, M. (2000). Deep dyslexia is right-hemisphere reading. *Brain and Language*, **71**, 299–309.

Coltheart, M., Rastle, K., Perry, C., Langdon, R., and Ziegler, J. (2001). DRC: A dual route cascaded model of visual word recognition and reading aloud. *Psychological Review*, **108**, 204–256.

Corina, D. P., Lawyer, L. A., and Cates, D. (2012). Cross-linguistic differences in the neural representation of human language: Evidence from users of signed languages. *Frontiers in Psychology*, **3**, 587.

Corina, D. P., McBurney, S. L., Dodrill, C., Hinshaw, K., Brinkley, J., and Ojemann, G. (1999). Functional roles of Broca's area and SMG: Evidence from cortical stimulation mapping in a deaf signer. *NeuroImage*, **10**, 570–581.

Danly, M., and Shapiro, B. (1982). Speech prosody in Broca's aphasia. *Brain and Language*, **16**, 171–190.

Dehaene, S., Cohen, L., Morais, J., and Kolinsky, R. (2015). Illiterate to literate: Behavioural and cerebral changes induced by reading acquisition. *Nature Reviews Neuroscience*, **16**(4), 234–244.

Dehaene, S., Pegado, F., Braga, L. W., Ventura, P., Nunes Filho, G., Jobert, A., et al. (2010). How learning to read changes the cortical networks for vision and language. *Science*, **330**(6009), 1359–1364.

Delis, D. C., Wapner, W., Gardner, H., and Moses, J. A. (1983). The contribution of the

right hemisphere to the organization of paragraphs. *Cortex*, **19**, 43–50.

De Renzi, E. (1980). The Token Test and the Reporter's Test: A measure of verbal input and a measure of verbal output. In M. T. Sarno and O. Hook (eds.), *Aphasia: Assessment and treatment*. New York: Masson.

De Renzi, E., Faglioni, P., Scotti, G., and Spinnler, H. (1972). Impairment in associating colour to form, concomitant with aphasia. *Brain*, **95**(2), 293–304.

Devlin, J. T., and Watkins, K. E. (2007). Stimulating language: Insights from TMS. *Brain: A Journal of Neurology*, **130**(Pt. 3), 610–622, figure 2, page 617.
<http://doi.org/10.1093/brain/awl331>

Diaz, M. T., and Hogstrom, L. J. (2011). The influence of context on hemispheric recruitment during metaphor processing. *Journal of Cognitive Neuroscience*, **23**(11), 3586–3597.

Dien, J. (2009). The neurocognitive basis of reading single words as seen through early latency ERPs: A model of converging pathways. *Biological Psychology*, **80**, 10–22.

Dronkers, N. F. (2000). The pursuit of brain–language relationships. *Brain and Language*, **71**, 59–61.

Dronkers, N. F., Plaisant, O., Iba-Zizen, M. T., and Cabanis, E. A. (2007). Paul Broca's historic cases: High-resolution MR imaging of the brain of Leborgne and Lelong. *Brain*, **130**, 1432–1441.

Emmorey, K., Mehta, S., and Grabowski, T. J. (2007). The neural correlates of sign versus word production. *NeuroImage*, **36**, 202–208.

Fadiga, L., Craighero, L., and D'Ausilio, A. (2009). Broca's area in language, action, and music. *Annals of the New York Academy of Sciences*, **1169**, 448–458.

Federmeier, K. D. (2007). Thinking ahead: The role and roots of prediction in language comprehension. *Psychophysiology*, **44**, 491–505.

Ferstl, E. C., Neumann, J., Bogler, C., and von Cramon, D. Y. (2008). The extended language network: A meta-analysis of neuroimaging studies on text comprehension. *Human Brain Mapping*, **29**, 581–593.

Fiez, J. A., and Petersen, S. E. (1998). Neuroimaging studies of word reading. *Proceedings of the National Academy of Sciences*, **95**, 914–921.

Fiez, J. A., Tallal, P., Raichle, M. E., Miezin, F. M., Katz, W. F., and Petersen, S. E. (1995). PET studies of auditory and phonological processing: Effects of stimulus characteristics and task demands. *Journal of Cognitive Neuroscience*, **7**, 357–375.

Fiez, J. A., Tranel, D., Seager-Frerichs, D., and Damasio, H. (2006). Specific reading and phonological processing deficits are associated with damage to the left frontal operculum. *Cerebral Cortex*, **42**, 624–643.

Foldi, N. S. (1987). Appreciation of pragmatic interpretation of indirect commands: Comparison of right and left brain-damaged patients. *Brain and Language*, **31**, 88–108.

Fridriksson, J., Yourganov, G., Bonilha, L., Basilakos, A., Ouden, Den, D.-B., and Rorden, C. (2016). Revealing the dual streams of speech processing. *Proceedings of the National Academy of Sciences*, **113**(52), 15108–15113.

Friederici, A. D., Hahne, A., and Mecklinger, A. (1996). Temporal structure of syntactic parsing: Early and late event-related brain potential effects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **22**, 1219–1248.

Friederici, A. D., and Gierhan, S. M. E. (2013). The language network. *Current Opinion in Neurobiology*, **23**(2), 250–254.

Frith, C. D., Friston, K. J., Liddle, P. F., and Frackowiak, R. S. J. (1991). A PET study

of word finding. *Neuropsychologia*, **29**, 1137–1148.

Giussani, C., Roux, F. E., Lubrano, V., Gaini, S. M., and Bello, L. (2007). Review of language organisation in bilingual patients: What can we learn from direct brain mapping? *Acta Neurochirurgica*, **149**, 1109–1116.

Goel, V., and Dolan, R. J. (2001). The functional anatomy of humor: Segregating cognitive and affective components. *Nature Neuroscience*, **4**, 237–238.

Golestani, N., Molko, N., Deheane, S., Le Bihan, D., and Pallier, C. (2007). Brain structure predicts learning of foreign speech sounds. *Cerebral Cortex*, **17**, 575–582.

Golestani, N., and Zatorre, R. J. (2004). Learning new sounds of speech: Reallocation of neural substrates. *NeuroImage*, **21**, 494–506.

Goodglass, H. (1976). Agrammatism. In H. Whitaker and H. A. Whitaker (eds.), *Studies in neurolinguistics* (pp. 237–260). New York: Academic Press.

Gough, P.M., Nobre, A.C., Devlin, J.T. (2005). Dissociating linguistic processes in the left inferior frontal cortex with transcranial magnetic stimulation. *Journal of Neuroscience*, **25**, 8010–8016.

Graves, W. W., Desai, R., Humphries, C., Seidenberg, M. S., and Binder, J. R. (2010). Neural systems for reading aloud: A multiparametric approach. *Cerebral Cortex*, **20**(8), 1799–1815.

Greenblatt, S. H. (1973). Alexia without agraphia or hemianopia. Anatomical analysis of an autopsied case. *Brain*, **96**, 307–316.

Grodzinsky, Y., and Friederici, A. D. (2006). Neuroimaging of syntax and syntactic processing. *Current Opinion in Neurobiology*, **16**, 240–246.

Grote, C. L., Wierenga, C., and Smith, M. C. (1999). Wada difference a day makes:

Interpretive cautions regarding same-day injections. *Neurology*, **52**, 1577–1582.

Hagoort, P., and Brown, C. (2000a). ERP effects of listening to speech: Semantic ERP effects. *Neuropsychologia*, **38**(11), 1518–1530.

Hagoort, P., and Brown, C. (2000b). ERP effects of listening to speech compared to reading: The P600/SPS to syntactic violations in spoken sentences and rapid serial visual presentation. *Neuropsychologia*, **38**(11), 1531–1549.

Hamberger, M. J. (2007). Cortical language mapping in epilepsy: A critical review. *Neuropsychology Review*, **17**, 477–489.

Hécaen, H., and Kremin, H. (1976). Neurolinguistic research on reading disorder from left hemisphere lesions: Aphasic and “pure” alexias. In H. A. Whitaker and H. Whitaker (eds.), *Studies in neurolinguistics II* (pp. 269–329). New York: Academic Press.

Hickok, G., and Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition*, **92**(1–2), 67–99.

Hickok, G., and Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, **8**(5), 393–402.

Hickok, G., Love-Geffen, T., and Klima, E. S. (2002). Role of the left hemisphere in sign language comprehension. *Brain and Language*, **82**(2), 167–178.

Hickok, G., Wilson, M., Clark, K., Klima, E. S., Kritchevsky, M., and Bellugi, U. (1999). Discourse deficits following right hemisphere damage in deaf signers. *Brain and Language*, **66**(2), 233–248.

Hillis, A. E. (2007). Aphasia: Progress in the last quarter of a century. *Neurology*, **69**, 200–213.

Hoffmann, M., and Chen, R. (2013). The spectrum of aphasia subtypes and etiology in

subacute stroke. *Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association*, **22**(8), 1385–1392.

Hope, T. M. H., Parker Jones, O., Grogan, A., Crinion, J., Rae, J., Ruffle, L., et al. (2015). Comparing language outcomes in monolingual and bilingual stroke patients. *Brain: A Journal of Neurology*, **138**(Pt. 4), 1070–1083.

Ihara, A. S., Mimura, T., Soshi, T., Yorifuji, S., Hirata, M., Goto, T., et al. (2015). Facilitated lexical ambiguity processing by transcranial direct current stimulation over the left inferior frontal cortex. *Journal of Cognitive Neuroscience*, **27**(1), 26–34.

Ino, T., Nakai, R., Azuma, T., Kimura, T., and Fukuyama, H. (2009). Recognition and reading aloud of kana and kanji word: An fMRI study. *Brain Research Bulletin*, **78**, 232–239.

Jobard, G., Crivello, F., and Tzourio-Mazoyer, N. (2003). Evaluation of the dual-route theory of reading: A metanalysis of 35 neuroimaging studies. *NeuroImage*, **20**, 693–712.

Jung, H., Sontag, S., Park, Y. S., and Loui, P. (2015). Rhythmic Effects of Syntax Processing in Music and Language. *Frontiers in Psychology*, **6**, 1762.

Jung-Beeman, M. (2005). Bilateral brain processes for comprehending natural language. *Trends in Cognitive Sciences*, **9**, 512–518.

Kaplan, J. A., Brownell, H. H., Jacobs, J. R., and Gardner, H. (1990). The effects of right hemisphere damage on the pragmatic interpretation of conversational remarks. *Brain and Language*, **38**, 315–333.

Kawahata, N., Nagata, K., and Shishido, F. (1988). Alexia with agraphia due to the left posterior inferior temporal lobe lesion: Neuropsychological analysis and its pathogenetic mechanisms. *Brain and Language*, **33**, 296–310.

Kawamura, M., Hirayama, K., Hasegawa, K., Takahashi, N., and Yamaura, A. (1987).

Alexia with agraphia of kanji (Japanese morphograms). *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 1125–1129.

Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., et al. (1998). Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron*, **20**(5), 927–936.

Khedr, E. M., Hamed, E., Said, A., and Basahi, J. (2002). Handedness and language cerebral lateralization. *European Journal of Applied Physiology*, **87**, 469–473.

Kim, A., and Osterhout, L. (2005). The independence of combinatory semantic processing: Evidence from event-related potentials. *Journal of Memory and Language*, **52**, 205–225.

Kircher, T. T. J., Brammer, M., Andreu, N. T., Steven, C. R., Williams, S. C. R., and McGuire, P. K. (2001). Engagement of right temporal cortex during processing of linguistic context. *Neuropsychologia*, **39**(8), 798–809.

Klein, D., Mok, K., Chen, J.-K., Watkins, K. (2014). Age of language learning shapes brain structure: A cortical thickness study of bilingual and monolingual individuals. *Brain and Language*, **131**, 20–24.

Kraus, N., and Slater, J. (2016). Beyond words: How humans communicate through sound. *Annual Review of Psychology*, **67**, 83–103.

Kroll, J. F., and Bialystok, E. (2013). Understanding the consequences of bilingualism for language processing and cognition. *Journal of Cognitive Psychology*, **25**(5).

Kronbichler, M., Klackl, J., Richlan, F, Schurz, M., Staffen, W., Ladurner, G., and Wimmer, H. (2009). On the functional neuroanatomy of visual word processing: Effects of case and letter deviance. *Journal of Cognitive Neuroscience*, **21**, 222–229.

Kuperberg, G. (2007). Neural mechanisms of language comprehension: Challenges to syntax. *Brain Research*, **1146**, 23–49.

Lai, V. T., van Dam, W., Conant, L. L., Binder, J. R., and Desai, R. H. (2015). Familiarity differentially affects right hemisphere contributions to processing metaphors and literals. *Frontiers in Human Neuroscience*, **9**, 44.

Li, P., Legault, J., and Litcofsky, K. A. (2014). Neuroplasticity as a function of second language learning: Anatomical changes in the human brain. *Cortex*, **58**, 301–324.

Lindell, A. K. (2006). In your right mind: Right hemisphere contributions to language processing and production. *Neuropsychology Review*, **16**, 131–148.

Liu, H., and Cao, F. (2016). L1 and L2 processing in the bilingual brain: A meta-analysis of neuroimaging studies. *Brain and Language*, **159**, 60–73.

Lorenzen, B., and Murray, L. L. (2008). Bilingual aphasia: A theoretical and clinical review. *American Journal of Speech-Language Pathology*, **17**, 299–317.

Lucas, T. H., McKhann, G. M., and Ojemann, G. A. (2004). Functional separation of languages in the bilingual brain: A comparison of electrical stimulation language mapping in 25 bilingual patients and 117 monolingual control patients. *Journal of Neurosurgery*, **101**, 449–457.

Luk, G., Bialystok, E., Craik, F. I. M., and Grady, C. L. (2011). Lifelong bilingualism maintains white matter integrity in older adults. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **31**(46), 16808–16813.

MacSweeney, M., Capek, C. M., Campbell, R., and Woll, B. (2008). The signing brain: The neurobiology of sign language. *Trends in Cognitive Sciences*, **12**(11), 432–440.

Maess, B., Koelsch, S., Gunter, T. C., and Friederici, A. D. (2001). Musical syntax is processed in Broca's area: An MEG study. *Nature Neuroscience*, **4**, 540–545.

Mainy, N., Jung, J., Baciú, M., Kahane, P., Schoendorff, B., Minotti, L., et al. (2008). Cortical dynamics of word recognition. *Human Brain Mapping*, **29**, 1215–1230.

Marsolek, C. J., and Deason, R. G. (2007). Hemispheric asymmetries in visual word-form processing: Progress, conflict, and evaluating theories. *Brain and Language*, **103**(3), 304–307; author reply 308–312. <http://doi.org/10.1016/j.bandl.2007.02.009>

Martin, C. D., Dering, B., Thomas, E. M., and Thierry, G. (2009). Brain potentials reveal semantic priming in both the “active” and the “non-attended” language of early bilinguals. *NeuroImage*, **47**, 326–333.

McCandliss, B. D., Cohen, L., and Dehaene, S. (2003). The visual word form area: Expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences*, **7**, 293–299.

McGettigan, C., and Scott, S. K. (2012). Cortical asymmetries in speech perception: What’s wrong, what’s right and what’s left? *Trends in Cognitive Sciences*, **16**(5), 269–276.

Mechelli, A., Crinion, J. T., Long, S., Friston, K. J., Lambon Ralph, M. A., Patterson, K., McClelland, J. L., and Price, C. J. (2005). Dissociating reading processes on the basis of neuronal interactions. *Journal of Cognitive Neuroscience*, **17**, 1753–1756.

Mechelli, A., Crinion, J. T., Noppeney, U., O’Doherty, J., Ashburner, J., Frackowiak, R. S., and Price, C. J. (2004). Neurolinguistics: Structural plasticity in the bilingual brain. *Nature*, **431**, 757.

Miceli, G., Gainotti, G., Caltagirone, C., and Masullo, C. (1980). Some aspects of phonological impairment in aphasia. *Brain and Language*, **11**, 159–169.

Merrett, D. L., Peretz, I., and Wilson, S. J. (2014). Neurobiological, cognitive, and emotional mechanisms in melodic intonation therapy. *Frontiers in Human Neuroscience*, **8**, 401. <http://doi.org/10.3389/fnhum.2014.00401>

Mobbs, D., Greicius, M. D., Abdel-Azim, E., Menon, V., and Reiss, A. L. (2003). Humor modulates the mesolimbic reward centers. *Neuron*, **40**, 1041–1048.

Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W., and Davis, K. R. (1978). Broca aphasia: Pathologic and clinical. *Neurology*, **28**, 311–324.

Mongelli, V., Dehaene, S., Vinckier, F., Peretz, I., Bartolomeo, P., and Cohen, L. (2016). Music and words in the visual cortex: The impact of musical expertise. *Cortex* (in press).

Morton, J., and Patterson, K. E. (1980). A new attempt at interpretation, or, an attempt at a new interpretation. In M. Coltheart, K. E. Patterson, and J. C. Marshall (eds.), *Deep dyslexia*. London: Routledge and Kegan Paul.

Morton, J. B. (2010). Language, bilingualism, and executive functioning in early development. *Psychological Reports*, **107**(3), 888–890.

Moya, K. L., Benowitz, L. I., Levine, D. N., and Finklestein, S. (1986). Covariant defects in visuospatial abilities and recall of verbal narrative after right hemisphere stroke. *Cortex*, **22**, 381–397.

Neville, H. J., Bavelier, D., Corina, D., Rauschecker, J., Karni, A., Lalwani, A., et al. (1998). Cerebral organization for language in deaf and hearing subjects: Biological constraints and effects of experience. *Proceedings of the National Academy of Sciences*, **95**, 922–929.

Newman, A. J., Bavelier, D., Corina, D., Jezard, P., and Neville, H. J. (2002). A critical period for right hemisphere recruitment in American Sign Language processing. *Nature Neuroscience*, **5**(1), 76–80.

Nichelli, P., Grafman, J., Pietrini, P., Clark, K., Lee, K. Y., and Miletich, R. (1995). Where the brain appreciates the moral of a story. *NeuroReport*, **6**, 2309–2313.

Nichols, E. S., and Joanisse, M. F. (2016). Functional activity and white matter microstructure reveal the independent effects of age of acquisition and proficiency on second-language learning. *NeuroImage*, **143**, 15–25.

Obert, A., Gierski, F., Calmus, A., Portefaix, C., Declercq, C., Pierot, L., and Caillies, S. (2014). Differential bilateral involvement of the parietal gyrus during predicative metaphor processing: An auditory fMRI study. *Brain and Language*, **137**, 112–119.

Osterhout, L., and Holcomb, P. J. (1992). Event-related potentials elicited by syntactic anomaly. *Journal of Memory and Language*, **31**, 785–806.

Palomar-García, M.-Á., Bueichekú, E., Avila, C., Sanjuan, A., Strijkers, K., Ventura-Campos, N., and Costa, A. (2015). Do bilinguals show neural differences with monolinguals when processing their native language? *Brain and Language*, **142**, 36–44.

Paradis, M., Hagiwara, H., and Hildebrandt, N. (1985). *Neurolinguistic aspects of the Japanese writing system*. New York: Academic Press.

Patel, A. D. (2008). *Music, language, and the brain*. New York: Oxford University Press.

Patterson, K. (1982). Reading and phonological coding. In A. W. Ellis (ed.), *Normality and pathology in cognitive functions* (pp. 77–112). New York: Academic Press.

Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., Cappa, S. F., et al. (2000). A cultural effect on brain function. *Nature Neuroscience*, **3**, 91–96.

Pell, M. D. (2006). Judging emotion and attitudes from prosody following brain damage. *Progress in Brain Research*, **156**, 303–317.

Peretz, I., and Zatorre, R. J. (2005). Brain organization for music processing. *Annual Review of Psychology*, **56**, 89–114.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., and Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, **331**, 585–589.

Petersen, S. E., Fox, P. T., Snyder, A. Z., and Raichle, M. E. (1990). Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science*, **249**, 1041–1044.

Petito, L. A., Zatorre, R. J., Gauna, K., Nikelski, E. J., Dostie, D., and Evans, A. C. (2000). Speech-like cerebral activity in profoundly deaf people processing signed languages: Implications for the neural basis of human language. *Proceedings of the National Academy of Sciences*, **97**, 13961–13966.

Pitchford, N. J., Funnell, E., de Haan, B., and Morgan, P. S. (2007). Right-hemisphere reading in a case of developmental deep dyslexia. *Quarterly Journal of Experimental Psychology*, **60**, 1187–1196.

Pliatsikas, C., Moschopoulou, E., and Saddy, J. D. (2015). The effects of bilingualism on the white matter structure of the brain. *Proceedings of the National Academy of Sciences*, **112**(5), 1334–1337.

Pliatsikas, C., DeLuca, V., Moschopoulou, E., and Saddy, J. D. (2017). Immersive bilingualism reshapes the core of the brain. *Brain Structure and Function*, **222**(4), 1785–1795.

Poeppel, D. (2003) The analysis of speech in different temporal integration windows: Cerebral lateralization as “asymmetric sampling in time.” *Speech Communication*, **41**, 245–255.

Poeppel, D. (2014). The neuroanatomic and neurophysiological infrastructure for speech and language. *Current Opinion in Neurobiology*, **28**, 142–149.

Poizner, H., Klima, E. S., and Bellugi, U. (1987). What the hands reveal about the brain. Cambridge, MA: MIT Press.

Połczyn'ska, M. M., Benjamin, C. F. A., Moseley, B. D., Walshaw, P., Eliashiv, D., Vigil, C., et al. (2015). Role of the Wada test and functional magnetic resonance imaging in preoperative mapping of language and memory: Two atypical cases. *Neurocase*, **21**(6), 707–720.

Prat, C. S., Mason, R. A., and Just, M. A. (2012). An fMRI investigation of analogical mapping in metaphor comprehension: The influence of context and individual cognitive capacities on processing demands. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, **38**(2), 282–294.

Price, C. J. (1998). The functional anatomy of word comprehension and production. *Trends in Cognitive Sciences*, **2**, 281–288.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *NeuroImage*, **62**(2), 816–847.

Price, C. J., Gorno-Tempini, M. L., Graham, K. S., Biggio, N., Mechelli, A., Patterson, K., and Noppeney, U. (2003). Normal and pathological reading: Converging data from lesion and imaging studies. *NeuroImage*, **20**(Suppl. I), S30–S41.

Price, C. J., Moore, C. J., Humphreys, G. W., and Wise, R. J. S. (1997). Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience*, **9**, 727–733.

Raichle, M. E., Fiez, J. A., Videen, T. O., MacLeod, A.-M. K., Pardo, J. V., Fox, P. T., and Petersen, S. E. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex*, **4**(1), 8–26.

Rapcsak, S. Z., Henry, M. L., Teague, S. L., Carnahan, S. D., and Beeson, P. M. (2007).

Do dual-route models accurately predict reading and spelling performance in individuals with acquired alexia and agraphia? *Neuropsychologia*, **45**, 2519–2524.

Rasmussen, T., and Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech function. *Annals of the New York Academy of Sciences*, **299**, 355–369.

Rehak, A., Kaplan, J. A., and Gardner, H. (1992). Sensitivity to conversational deviance in right-hemisphere-damaged patients. *Brain and Language*, **42**, 203–217.

Richardson, F. M., and Price, C. J. (2009). Structural MRI studies of language function in the undamaged brain. *Brain Structure and Function*, **213**, 511–523.

Rilling, J. K., Glasser, M. F., Preuss, T. M., Ma, X., Zhao, T., Hu, X., and Behrens, T. E. (2008). The evolution of the arcuate fasciculus revealed with comparative DTI. *Nature Neuroscience*, **11**, 426–428.

Ripamonti, E., Aggujaro, S., Molteni, F., Zonca, G., Frustaci, M., and Luzzatti, C. (2014). The anatomical foundations of acquired reading disorders: A neuropsychological verification of the dual-route model of reading. *Brain and Language*, **134**, 44–67.

Riva, M., Casarotti, A., Comi, A., Pessina, F., and Bello, L. (2016). Brain and music: An intraoperative stimulation mapping study of a professional opera singer. *World Neurosurgery*, **93**, 486.e13–486.e18. <http://doi.org/10.1016/j.wneu.2016.06.130>

Robson, H., Keidel, J. L., Lambon Ralph, M. A., and Sage, K. (2012). Revealing and quantifying the impaired phonological analysis underpinning impaired comprehension in Wernicke's aphasia. *Neuropsychologia*, **50**(2), 276–288.

Rodel, M., Cook, N. D., Regard, M., and Landis, T. (1992). Hemispheric dissociation in judging semantic relations: Complementarity for close and distant associates. *Brain and Language*, **43**, 448–459.

Román, P., González, J., Ventura-Campos, N., Rodríguez-Pujadas, A., Sanjuán, A., and Ávila, C. (2015). Neural differences between monolinguals and early bilinguals in their native language during comprehension. *Brain and Language*, **150**, 80–89.

Ross, E. D., and Monnot, M. (2008). Neurology of affective prosody and its functional-anatomic organization in right hemisphere. *Brain and Language*, **104**, 51–74.

Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K., Maisog, J. M., and Andreason, P. (1997). Phonological and orthographic components of word recognition: A PET-rCBF study. *Brain*, **120**, 739–759.

Sakai, K. L., Nauchi, A., Tatsuno, Y., Hirano, K., Muraishi, Y., Kimura, M., Bostwick, M., and Yusa, N. (2009). Distinct roles of left inferior frontal regions that explain individual differences in second language acquisition. *Human Brain Mapping*, **30**, 2440–2452.

Sakurai, Y., Momose, T., Iwata, M., Sudo, Y., Ohtomo, K., and Kanazawa, I. (2000). Different cortical activity in reading Kanji words, Kana words and Kana nonwords. *Cognitive Brain Research*, **9**(1), 111–115.

Salmelin, R., and Kujala, J. (2006). Neural representation of language: Activation versus long-range connectivity. *Trends in Cognitive Sciences*, **10**, 519–525.

Sammler, D., Grosbras, M.-H., Anwender, A., Bestelmeyer, P. E. G., and Belin, P. (2015). Dorsal and ventral pathways for prosody. *Current Biology: CB*, **25**(23), 3079–3085.

Sasanuma, S. (1980). Acquired dyslexia in Japanese: Clinical features and underlying mechanisms. In M. Coltheart, K. E. Patterson, and J. C. Marshall (eds.), *Deep dyslexia*. London: Routledge and Kegan Paul.

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., et al.

(2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences*, **105**(46), 18035–18040.

Schneiderman, E. I., Murasugi, K. G., and Saddy, J. D. (1992). Story arrangement ability in right brain-damaged patients. *Brain and Language*, **43**, 107–120.

Schön, D., Anton, J. L., Roth, M., and Besson, M. (2002). An fMRI study of music sight-reading. *NeuroReport*, **13**, 2285–2289.

Sergent, J., Zuck, E., Terriah, S., and Macdonald, B. (1992). Distributed neural network underlying musical sight-reading and keyboard performance. *Science*, **257**, 106–109.

Shallice, T. (1981). Phonological agraphia and the lexical route in writing. *Brain*, **104**, 413–429.

Shallice, T., Warrington, E. K., and McCarthy, R. (1983). Reading without semantics. *Quarterly Journal of Experimental Psychology*, **35A**, 111–138.

Slevc, L. R., and Okada, B. M. (2015). Processing structure in language and music: A case for shared reliance on cognitive control. *Psychonomic Bulletin and Review*, **22**(3), 637–652.

Stewart, L. (2005). A neurocognitive approach to music reading. *Annals of the New York Academy of Sciences*, **1060**, 377–386.

Stewart, L., von Kriegstein, K., Warren, J. D., and Griffiths, T. D. (2006). Music and the brain: Disorders of musical listening. *Brain*, **129**, 2533–2553.

St. George, M., Kutas, M., Martinez, A., and Sereno, M. I. (1999). Semantic integration in reading: Engagement on the right hemisphere during discourse processing. *Brain*, **122**, 1317–1325.

Stromswold, K., Caplan, D., Alpert, N., and Rauch, S. (1996). Localization of syntactic comprehension by positron emission tomography. *Brain and Language*, **52**, 452–473.

Tarkiainen, A., Helenius, P., Hansen, P. C., Cornelissen, P. L., and Salmelin, R. (1999). Dynamics of letter string perception in the human occipitotemporal cortex. *Brain*, **122**, 2119–2131.

Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L. W., and Dehaene, S. (2014). Learning to read improves the structure of the arcuate fasciculus. *Cerebral Cortex*, **24**(4), 989–995.

Tippett, D. C., Niparko, J. K., and Hillis, A. E. (2014). Aphasia: Current concepts in theory and practice. *Journal of Neurology and Translational Neuroscience*, **2**(1), 1042.

Tyler, L. K., Marslen-Wilson, W. D., Randall, B., Wright, P., Devereux, B. J., Zhuang, J., et al. (2011). Left inferior frontal cortex and syntax: Function, structure and behaviour in patients with left hemisphere damage. *Brain: A Journal of Neurology*, **134**(Pt. 2), 415–431.

Usui, K., Ikeda, A., Nagamine, T., Matsushashi, M., Kinoshita, M., Mikuni, N., et al. (2009). Temporal dynamics of Japanese morphogram and syllabogram processing in the left basal temporal area studied by event-related potentials. *Journal of Clinical Neurophysiology*, **26**, 160–166.

van Heuven, W. J., Schriefers, H., Dijkstra, T., and Hagoort, P. (2008). Language conflict in the bilingual brain. *Cerebral Cortex*, **18**, 2706–2716.

van Petten, C., and Luka, B. J. (2006). Neural localization of semantic context effects in electromagnetic and hemodynamic studies. *Brain and Language*, **97**, 279–293.

Vigneau, M., Beauconsin, V., Hervé, P. Y., Duffau, H., Crivello, F., Houdé, O., Mazoyer, B., and Tzourio-Mazoyer, N. (2006). Meta-analyzing left hemisphere language areas:

Phonology, semantics, and sentence processing. *NeuroImage*, **30**, 1414–1432.

Vigneau, M., Beauconsin, V., Hervé, P.-Y., Jobard, G., Petit, L., Crivello, F., et al. (2011). What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. *NeuroImage*, **54**(1), 577–593.

von Stockert, T. R., and Bader, A. L. (1976). Some relations of grammar and lexicon in aphasia. *Cortex*, **12**, 49–60.

Vuong, L. C., and Martin, R. C. (2015). The role of LIFG-based executive control in sentence comprehension. *Cognitive Neuropsychology*, **32**(5), 243–265.

Wagner, A. D. (1999). Working-memory contributions to human learning and remembering. *Neuron*, **22**(1), 19–22.

Wandell, B. A. (2011). The neurobiological basis of seeing words. *Annals of the New York Academy of Sciences*, **1224**(1), 63–80.

Wandell, B. A., and Yeatman, J. D. (2013). Biological development of reading circuits. *Current Opinion in Neurobiology*, **23**(2), 261–268.

Watkins, K., and Paus, T. (2004). Modulation of motor excitability during speech perception: The role of Broca's area. *Journal of Cognitive Neuroscience*, **16**, 978–987.

Weber, K., Luther, L., Indefrey, P., and Hagoort, P. (2016). Overlap and differences in brain networks underlying the processing of complex sentence structures in second language users compared with native speakers. *Brain Connectivity*, **6**(4), 345–355.

Weintraub, S., Mesulam, M.-M., and Kramer, L. (1981). Disturbances in prosody: A right hemisphere contribution to language. *Archives of Neurology*, **38**, 742–744.

Winner, E., and Gardner, H. (1977). The comprehension of metaphor in brain-damaged patients. *Brain*, **100**, 719–727.

Witteman, J., van IJzendoorn, M. H., van de Velde, D., van Heuven, V. J. J. P., and Schiller, N. O. (2011). The nature of hemispheric specialization for linguistic and emotional prosodic perception: A meta-analysis of the lesion literature. *Neuropsychologia*, **49**(13), 3722–3738.

Wlotko, E. W., and Federmeier, K. D. (2013). Two sides of meaning: The scalp-recorded n400 reflects distinct contributions from the cerebral hemispheres. *Frontiers in Psychology*, **4**, 181. <http://doi.org/10.3389/fpsyg.2013.00181>

Wylie, E., Luders, H., and Murphy, D. (1990). Intracarotid amobarbital (Wada) test for language dominance: Correlation with results of cortical stimulation. *Epilepsia*, **31**(2), 156–161.

Yourganov, G., Smith, K. G., Fridriksson, J., and Rorden, C. (2015). Predicting aphasia type from brain damage measured with structural MRI. *Cortex*, **73**, 203–215, figure 4, page 212.

Zaidel, E. (1990). The saga of right-hemisphere reading. In C. Trevarthen (ed.), *Brain circuits and functions of the mind: Essays in honor of Roger W. Sperry* (pp. 304–319). Cambridge: Cambridge University Press.

Zatorre, R. J., and Gandour, J. T. (2008). Neural specializations for speech and pitch: Moving beyond the dichotomies. *Philosophical Transactions of the Royal Society of London, Series B*, **363**(1493), 1087–1104.

Zatorre, R. J., Meyer, E., Gjedde, A., and Evans, A. C. (1996). PET studies of phonetic processing of speech: Review, replication, and reanalysis. *Cerebral Cortex*, **6**, 21–30.

Chapter 9

Addis, D. R., and Schacter, D. L. (2011). The hippocampus and imagining the future: Where do we stand? *Frontiers in Human Neuroscience*, **5**, 173.

Addis, D. R., Wong, A. T., and Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, **45**, 1363–1377.

Albert, M. S., Butters, N., and Levin, J. (1979). Temporal gradients in the retrograde amnesia of patients with Korsakoff's disease. *Archives of Neurology*, **36**, 211.

Anderson, M. C., Bunce, J. G., and Barbas, H. (2016). Prefrontal-hippocampal pathways underlying inhibitory control over memory. *Neurobiology of Learning and Memory*, **134**(Pt. A), 145–161.

Annese, J., Schenker-Ahmed, N. M., Bartsch, H., Maechler, P., Sheh, C., Thomas, N., et al. (2014). Postmortem examination of patient H.M.'s brain based on histological sectioning and digital 3D reconstruction. *Nature Communications*, **5**, 3122.

<http://doi.org/10.1038/ncomms4122>

Axmacher, N., Draguhn, A., Elger, C. E., and Fell, J. (2009). Memory processes during sleep: Beyond the standard consolidation theory. *Cellular and Molecular Life Sciences*, **66**, 2285–2297.

Baddeley, A. D. (1986). *Working memory*. Oxford: Oxford University Press.

Baddeley, A. D., and Hitch, G. (1974). Working memory. In G. A. Bower (ed.), *The psychology of learning and motivation* (pp. 47–90). New York: Academic Press.

Bakker, A., Kirwan, C. B., Miller, M., and Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus, *Science* **319**(5870), 1640–1642.

Batterink, L. J., Creery, J. D., and Paller, K. A. (2016). Phase of spontaneous slow oscillations during sleep influences memory-related processing of auditory cues. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **36**(4), 1401–1409.

Batterink, L. J., and Paller, K. A. (2017). Sleep-based memory processing facilitates grammatical generalization: Evidence from targeted memory reactivation. *Brain and Language*, **167**, 83–93.

Baumann, O., Chan, E., and Mattingley, J. B. (2010). Dissociable neural circuits for encoding and retrieval of object locations during active navigation in humans. *NeuroImage*, **49**(3), 2816–2825.

Bayley, P. J., Hopkins, R. O., and Squire, L. R. (2006). The fate of old memories after medial temporal lobe damage. *Journal of Neuroscience*, **26**(51), 13311–13317.

Bayley, P. J., O'Reilly, R. C., Curran, T., and Squire, L. R. (2008). New semantic learning in patients with large medial temporal lobe lesions. *Hippocampus*, **18**, 575–583.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., and Damasio, A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, **269**, 1115–1118.

Berryhill, M. E. (2012). Insights from neuropsychology: Pinpointing the role of the posterior parietal cortex in episodic and working memory. *Frontiers in Integrative Neuroscience*, **6**, 31. <http://doi.org/10.3389/fnint.2012.00031>

Berryhill, M. E., Phuong, L., Picasso, L., Cabeza, R., and Olson, I. R. (2007). Parietal lobe and episodic memory: Bilateral damage causes impaired free recall of autobiographical memory. *Journal of Neuroscience*, **27**, 14415–14423.

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences*, **15**(11), 527–536.

Binney, R. J., Embleton, K. V., Jefferies, E., Parker, G. J. M., and Ralph, M. A. L. (2010). The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: Evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. *Cerebral Cortex*, **20**(11), 2728–2738.

Blumenfeld, R. S., Lee, T. G., and D'Esposito, M. (2014). The effects of lateral prefrontal transcranial magnetic stimulation on item memory encoding. *Neuropsychologia*, **53**, 197–202.

Blumenfeld, R. S., and Ranganath, C. (2006). Dorsolateral prefrontal cortex promotes long-term memory formation through its role in working memory organization. *Journal of Neuroscience*, **26**, 916–925.

Blumenfeld, R. S., and Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: An integrative review of findings from neuropsychology and neuroimaging. *The Neuroscientist*, **13**, 280–291.

Bonnici, H. M., Kumaran, D., Chadwick, M. J., Weiskopf, N., Hassabis, D., and Maguire, E. A. (2012). Decoding representations of scenes in the medial temporal lobes. *Hippocampus*, **22**(5), 1143–1153.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science*, **281**(5380), 1151–1152.

Bright, P., Buckman, J., Fradera, A., Yoshimasu, H., Colchester, A. C., and Kopelman, M. D. (2006). Retrograde amnesia in patients with hippocampal, medial temporal, temporal lobe, or frontal pathology. *Learning and Memory*, **13**(5), 545–557.

Brooks, D. N., and Baddeley, A. (1976). What can amnesic patients learn? *Neuropsychologia*, **14**, 111–122.

Brown, A. S. (2002). Consolidation theory and retrograde amnesia in humans. *Psychonomic Bulletin and Review*, **9**, 403–425.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D., and Rosen, B. R. (1998). Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. *NeuroImage*, **7**(3), 151–162.

Burianova, H., McIntosh, A. R., and Grady, C. L. (2010). A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *NeuroImage*, **49**(1), 865–874.

Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, **25**(10), 1073–1188.

Cabeza, R., Ciaramelli, E., Olson, I. R., and Moscovitch, M. (2008). The parietal cortex and episodic memory: An attentional account. *Nature Reviews Neuroscience*, **9**(8), 613–625.

Cahill, L., Babinsky, R., Markowitsch, H. J., and McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature*, **377**(6547), 295–296.

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D., et al. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Science of the United States of America* **93**(15), 8016–8021.

Cahill, L., Weinberger, N. M., Roozendaal, B., and McGaugh, J. L. (1999). Is the amygdala a locus of “conditioned fear”? Some questions and caveats. *Neuron*, **23**(2), 227–228.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., and Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *The Journal of Neuroscience*, **20**(19), RC99.

Caramazza, A., Miceli, G., Silveri, M. C., and Laudanna, A. (1985). Reading mechanisms and the organization of the lexicon: Evidence from acquired dyslexia. *Cognitive Neuropsychology*, **2**, 81–114.

Cermak, L. S., Lewis, R., Butters, N., and Goodglass, H. (1973). Role of verbal mediation in performance of motor tasks by Korsakoff patients. *Perceptual and Motor Skills*, **37**, 259–262.

Ciaramelli, E., Grady, C. L., Levine, B., Ween, J., and Moscovitch, M. (2010). Top-down and bottom-up attention to memory are dissociated in posterior parietal cortex: Neuroimaging and neuropsychological evidence. *Journal of Neuroscience*, **30**, 4943–4956.

Cipolotti, L., and Bird, C. M. (2006). Amnesia and the hippocampus. *Current Opinion in Neurology*, **19**(6), 593–598.

Cohen, N. J., and Squire, L. R. (1980). Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, **210**, 207–210.

Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia*, **6**, 255–265.

Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H.M. *Seminars in Neurology*, **4**, 249–259.

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience*, **3**(2), 153–160.

Corkin, S., Amaral, D. G., Gilberto González, R., Johnson, K. A., and Hyman, B. T. (1997). H.M.'s medial temporal lobe lesion: Findings from magnetic resonance imaging. *Journal of Neuroscience*, **17**, 3964–3979.

Curran, T. (2000). Brain potentials of recollection and familiarity. *Memory and Cognition*, **28**, 923–938.

Curran, T., Schacter, D. L., Norman, K. A., and Galluccio, L. (1997). False recognition after a right frontal lobe infarction: Memory for general and specific information. *Neuropsychologia*, **35**(7), 1035–1049.

Depue, B. E. (2012). A neuroanatomical model of prefrontal inhibitory modulation of memory retrieval. *Neuroscience and Biobehavioral Reviews*, **36**(5), 1382–1399.

Depue, B. E., Curran, T., and Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*, **317**(5835), 215–219.

Depue, B. E., Orr, J. M., Smolker, H. R., Naaz, F., and Banich, M. T. (2015). The Organization of Right Prefrontal Networks Reveals Common Mechanisms of Inhibitory Regulation Across Cognitive, Emotional, and Motor Processes. *Cerebral Cortex*, **26**(4), 1634–1646.

D'Esposito, M., Cooney, J. W., Gazzaley, A., Gibbs, S. E., and Postle, B. R. (2006). Is the prefrontal cortex necessary for delay task performance? Evidence from lesion and fMRI data. *Journal of the International Neuropsychological Society*, **12**(2), 248–260.

D'Esposito, M., and Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annual Review of Psychology*, **66**(1), 115–142.

Diekelmann, S., and Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, **11**(2), 114–126. <http://doi.org/10.1038/nrn2762>

Doyon, J. (2008). Motor sequence learning and movement disorders. *Current Opinion in Neurology*, **21**, 478–483.

Drachman, D. A., and Arbit, J. (1966). Memory and hippocampal complex. II. Is memory a multiple process? *Archives of Neurology*, **15**, 52–61.

Dudai, Y., Karni, A., and Born, J. (2015). The consolidation and transformation of memory. *Neuron*, **88**(1), 20–32.

Dunn, J. C. (2004). Remember-know: A matter of confidence. *Psychological Review*, **111**, 524–542.

Dupont, S., van de Moortele, P. F., Samson, S., Hasboun, D., Poline, J. B., Adam, C., et al. (2000). Episodic memory in left temporal lobe epilepsy: A functional MRI study. *Brain*, **123**, 1722–1732.

Eichenbaum, H. (1999). Neurobiology: The topography of memory. *Nature*, **402**(6762), 597–599.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience*, **1**(1), 41–50.

Eichenbaum, H. (2014). Time cells in the hippocampus: A new dimension for mapping memories. *Nature Reviews Neuroscience*, **15**(11), 732–744.

Eichenbaum, H. (2017). Memory: Organization and control. *Annual Review of Psychology*, **68**, 19–45.

Eichenbaum, H., and Cohen, N. J. (2001). From conditioning to conscious recollection: Memory systems of the brain. New York: Oxford University Press.

Eichenbaum, H., Stewart, C., and Morris, R. G. M. (1990). Hippocampal representation in spatial learning. *Journal of Neuroscience*, **10**, 331–339.

Eichenbaum, H., Yonelinas, A. P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, **30**, 123–152.

Eldridge, L. L., Engel, S. A., Zeineh, M. M., Bookheimer, S. Y., and Knowlton, B. J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **25**(13), 3280–3286.

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., and Thompson-Schill, S. L. (2006). Interfering with theories of sleep and memory: Sleep, declarative memory, and associative interference. *Current Biology*, **16**, 1290–1294.

Ellenbogen, J. M., Payne, J. D., and Stickgold, R. (2006). The role of sleep in declarative memory consolidation: Passive, permissive, active or none? *Current Opinion in Neurobiology*, **16**, 716–722.

Eriksson, J., Vogel, E. K., Lansner, A., Bergström, F., and Nyberg, L. (2015). Neurocognitive architecture of working memory. *Neuron*, **88**(1), 33–46.

Fabiani, M., and Donchin, E. (1995). Encoding processes and memory organization: A model of the von Restorff effect. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **21**(1), 224–240.

Fernandez, G., Effer, A., Grunwald, T., Pezer, N., Lehnertz, K., Dimpelmann, M., et al. (1999). Real-time tracking of memory formation in the human rhinal cortex and hippocampus. *Science*, **285**(5433), 1582–1585.

Fischer, S., Hallschmid, M., Elsner, A. L., and Born, J. (2002). Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences*, **99**, 11987–11991.

Flament, D., Ellermann, J. M., Kim, S. G., Ugurbil, K., and Ebner, T. J. (1996). Functional magnetic resonance imaging of cerebellar activation during the learning of a visuo-motor dissociation task. *Human Brain Mapping*, **4**(3), 210–226.

Foerde, K., and Shohamy, D. (2011). The role of the basal ganglia in learning and memory: Insight from Parkinson's disease. *Neurobiology of Learning and Memory*, **96**(4), 624–636, figure 1, page 625.

Frank, M. J., O'Reilly, R., and Curran, T. (2006). When memory fails, intuition reigns: Midazolam enhances implicit inference in humans. *Psychological Science*, **17**, 700–707.

Fraser, L. M., O'Carroll, R. E., and Ebmeier, K. P. (2008). The effect of electroconvulsive therapy on autobiographical memory: A systematic review. *Journal of ECT*, **24**(1), 10–17.

Funahashi, S. (2006). Prefrontal cortex and working memory processes. *Neuroscience*, **139**, 251–261.

Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic "scotomas." *Journal of Neuroscience*, **13**(4), 1479–1497.

Gabrieli, J. D. (1998). Cognitive science of human memory. *Annual Review of Psychology*, **49**, 87–115.

Gabrieli, J. D., Cohen, N. J., and Corkin, S. (1988). The impaired learning of semantic knowledge following bilateral medial temporal-lobe resection. *Brain and Cognition*, **7**(2), 157–177.

Gabrieli, J. D. E., Fleischman, D. A., Keane, M. M., Reminger, S. L., and Morrell, F. (1995). Double dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychological Science*, **6**(2), 76–82.

Gaesser, B., Spreng, R. N., McLelland, V. C., Addis, D. R., and Schacter, D. L. (2013). Imagining the future: Evidence for a hippocampal contribution to constructive processing. *Hippocampus*, **23**(12), 1150–1161. <http://doi.org/10.1002/hipo.22152>

Gaffan, D. (1974). Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *Journal of Comparative and Physiological Psychology*, **86**, 1100–1109.

Gais, S., Lucas, B., and Born, J. (2006). Sleep after learning aids memory recall. *Learning and Memory*, **13**, 259–262.

Gershberg, F. B., and Shimamura, A. P. (1995). Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia*, **33**(10), 1305–1333.

Gilmore, A. W., Nelson, S. M., and McDermott, K. B. (2015). A parietal memory network revealed by multiple MRI methods. *Trends in Cognitive Sciences*, **19**(9), 534–543.

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Review of Neuroscience*, **11**, 137–156.

Goldman-Rakic, P. S. (1995). Anatomical and functional circuits in prefrontal cortex of nonhuman primates. Relevance to epilepsy. *Advances in Neurology*, **66**, 51–63.

Graf, P., Squire, L. R., and Mandler, G. (1984). The information that amnesic patients do not forget. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **10**(1), 164–178.

Grafton, S. T., Hazeltine, E., and Ivry, R. (1995). Functional mapping of sequence learning in normal humans. *Journal of Cognitive Neuroscience*, **7**(4), 497–510.

Grafton, S. T., Mazziotta, J. C., Presty, S., Friston, K. J., Frackowiak, R. S., and Phelps, M. E. (1992). Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *Journal of Neuroscience*, **12**(7), 2542–2548.

Grafton, S. T., Woods, R. P., and Tyszka, M. (1994). Functional imaging of procedural

motor learning: Relating cerebral blood flow with individual subject performance. *Human Brain Mapping*, **1**(3), 221–234.

Haist, F., Bowden Gore, J., and Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nature Neuroscience*, **4**(11), 1139–1145.

Halgren, E. (1984). Human hippocampal and amygdal recording and stimulation: Evidence for a neural model of recent memory. In L. R. Squire and N. Butters (eds.), *The neuropsychology of memory* (pp. 165–182). New York: Guilford Press.

Hartley, T., Lever, C., Burgess, N., and O'Keefe, J. (2014). Space in the brain: How the hippocampal formation supports spatial cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, **369**(1635), 20120510.

Haxby, J. V., Horwitz, B., Ungerleider, L. G., Maisog, J. M., Pietrini, P., and Grady, C. L. (1994). The functional organization of human extrastriate cortex: A PET-rCBF study of selective attention to faces and locations. *Journal of Neuroscience*, **14**(11), 6336–6353.

Hebben, N., Corkin, S., Eichenbaum, H., and Shedlack, K. (1985). Diminished ability to interpret and report internal states after bilateral medial temporal resection: Case H.M. *Behavioral Neuroscience*, **99**(6), 1031–1039.

Henderson, L. M., Weighall, A. R., Brown, H., and Gaskell, M. G. (2012). Consolidation of vocabulary is associated with sleep in children. *Developmental Science*, **15**(5), 674–687.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., and Dolan, R. J. (1999). Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging. *Journal of Neuroscience*, **19**(10), 3962–3972.

Insausti, R., Annese, J., Amaral, D. G., and Squire, L. R. (2013). Human amnesia and

the medial temporal lobe illuminated by neuropsychological and neurohistological findings for patient E.P. *Proceedings of the National Academy of Sciences*, **110**(21), E1953–1962.

Jacoby, L. L. (1984). Incidental versus intentional retrieval: Remembering and awareness as separate issues. In L. R. Squire and N. Butters (eds.), *Neuropsychology of memory* (pp. 145–156). New York: Guilford Press.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S., and Passingham, R. E. (1994). Motor sequence learning: A study with positron emission tomography. *Journal of Neuroscience*, **14**(6), 3775–3790.

Ji, D., and Wilson, M. A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature Neuroscience*, **10**, 100–107.

Johnsrude, I. S., Owen, A. M., White, N. M., Zhao, W. V., Bohbot, V. (2000). Impaired preference conditioning after anterior temporal lobe resection in humans. *Journal of Neuroscience*, **20**:2649–2656

Jonides, J., and Nee, D. E. (2006). Brain mechanisms of proactive interference in working memory. *Neuroscience*, **139**, 181–193.

Jung, R. E., Flores, R. A., and Hunter, D. (2016). A new measure of imagination ability: Anatomical brain imaging correlates. *Frontiers in Psychology*, **7**, 496.

Kapur, N. (1999). Syndromes of retrograde amnesia: A conceptual and empirical analysis. *Psychological Bulletin*, **125**, 800–825.

Kapur, N., and Brooks, D. J. (1999). Temporally-specific retrograde amnesia in two cases of discrete bilateral hippocampal pathology. *Hippocampus*, **9**(3), 247–254.

Karni, A., Meyer, G., Jezard, P., Adams, M. M., Turner, R., and Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill

learning. *Nature*, **377**, 155–158.

Keane, M. M., Clarke, H., and Corkin, S. (1992). Impaired perceptual priming and intact conceptual priming in a patient with bilateral posterior cerebral lesions. *Society for Neuroscience Abstracts*, **18**, 386.

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *NeuroImage*, **54**(3), 2446–2461.

Kleim, J. A., Lussnig, E., Schwarz, E. R., Comery, T. A., and Greenough, W. T. (1996). Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. *Journal of Neuroscience*, **16**(14), 4529–4535.

Knowlton, B. J., Mangels, J. A., and Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science*, **273**(5280), 1399–1402.

Knowlton, B. J., Squire, L. R., Paulsen, J. S., Swerdlow, N. R., Swenson, M., and Butters, N. (1996). Dissociations within nondeclarative memory in Huntington's disease. *Neuropsychology*, **10**, 538–548.

Konishi, S., Wheeler, M. E., Donaldson, D. I., and Buckner, R. L. (2000). Neural correlates of episodic retrieval success. *NeuroImage*, **12**(3), 276–286.

Kopelman, M. D., and Bright, P. (2012). On remembering and forgetting our autobiographical pasts: Retrograde amnesia and Andrew Mayes's contribution to neuropsychological method. *Neuropsychologia*, **50**(13), 2961–2972.

Kopelman, M. D., Bright, P., Fulker, H., Hinton, N., Morrison, A., and Verfaellie, M. (2009). Remote semantic memory in patients with Korsakoff's syndrome and herpes encephalitis. *Neuropsychology*, **23**(2), 144–157.

Kopelman, M. D., Stanhope, N., and Kingsley, D. (1999). Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions. *Neuropsychologia*, **37**(8),

939–958.

Kuhl, B. A., and Chun, M. M. (2014). Successful remembering elicits event-specific activity patterns in lateral parietal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **34**(23), 8051–8060.

Kumaran, D., Hassabis, D., and McClelland, J. L. (2016). What learning systems do intelligent agents need? Complementary learning systems theory updated. *Trends in Cognitive Sciences*, **20**(7), 512–534.

Kurczek, J., Wechsler, E., Ahuja, S., Jensen, U., Cohen, N. J., Tranel, D., and Duff, M. (2015). Differential contributions of hippocampus and medial prefrontal cortex to self-projection and self-referential processing. *Neuropsychologia*, **73**, 116–126.

LaBar, K. S., and Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience*, **7**, 54–64.

LaBar, K. S., LeDoux, J. E., Spencer, D. D., and Phelps, E. A. (1995). Impaired fear conditioning following unilateral temporal lobectomy in humans. *Journal of Neuroscience*, **15**, 6846–6855.

Lechowicz, M., Miller, L., Irish, M., Addis, D. R., Mohamed, A., and Lah, S. (2016). Imagining future events in patients with unilateral temporal lobe epilepsy. *The British Journal of Clinical Psychology*, **55**(2), 187–205.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, **23**, 155–184.

Lepage, M., Habib, R., and Tulving, E. (1998). Hippocampal PET activations of memory encoding and retrieval: The HIPER model. *Hippocampus*, **8**(4), 313–322.

Lewis-Peacock, J. A., and Postle, B. R. (2012). Decoding the internal focus of attention. *Neuropsychologia*, **50**(4), 470–478.

Lundqvist, M., Rose, J., Herman, P., Brincat, S. L., Buschman, T. J., and Miller, E. K. (2016). Gamma and beta bursts underlie working memory. *Neuron*, **90**(1), 152–164.

MacPherson, S. E., Turner, M. S., Bozzali, M., Cipolotti, L., and Shallice, T. (2016). The Doors and People Test: The effect of frontal lobe lesions on recall and recognition memory performance. *Neuropsychology*, **30**(3), 332–337.

<http://doi.org/10.1037/neu0000240>

Maguire, E. A., Henson, R. N., Mummery, C. J., and Frith, C. D. (2001). Activity in prefrontal cortex, not hippocampus, varies parametrically with the increasing remoteness of memories. *NeuroReport*, **12**(3), 441–444.

Manns, J. R., Howard, M., and Eichenbaum, H. (2007). Gradual changes in hippocampal activity support remembering the order of events. *Neuron*, **56**, 530–540.

Martone, M., Butters, N., Payne, M., Becker, J. T., and Sax, D. (1984). Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology*, **41**(9), 965–970.

Mayes, A., Montaldi, D., and Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Science*, **11**, 126–135.

Mayes, A. R., Downes, J. J., McDonald, C., Poole, V., Rooke, S., Sagar, H. J., and Meudell, P. R. (1994). Two tests for assessing remote public knowledge: A tool for assessing retrograde amnesia. *Memory*, **2**(2), 183–210.

McDermott, K. B., Buckner, R. L., Peterson, S. E., Kelley, W. M., and Sanders, A. L. (1999). Set- and code-specific activation in the frontal cortex: An fMRI study of encoding and retrieval of faces and words. *Journal of Cognitive Neuroscience*, **11**(6), 631–640.

Meeter, M., Eijsackers, E. V., and Mulder, J. L. (2006). Retrograde amnesia for

autobiographical memories and public events in mild and moderate Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, **28**(6), 914–927.

Milner, B. (1962). Les troubles de la mémoire accompagnant des lésions hippocampiques bilatérales [Memory troubles accompanying bilateral hippocampal lesions]. In P. Passouant (ed.), *Physiologie de l'hippocampe* [Physiology of the hippocampus] (pp. 257–272). Paris: Centre National de la Recherche Scientifique.

Milner, B., Corkin, S., and Teuber, H. L. (1968). Further analysis of the hippocampal amnesia syndrome. *Neuropsychologia*, **6**, 215–234.

Mishkin, M. (1982). A memory system in the monkey. *Philosophical Transactions of the Royal Society of London, Series B*, **298**, 85–95.

Mishkin, M., and Delacour, J. (1975). An analysis of short-term visual memory in the monkey. *Journal of Experimental Psychology: Animal Behavior Processes*, **104**, 326–334.

Morris, R. G. M. (1981). Spatial localization does not require the presence of local cues. *Learning and Motivation*, **12**, 239–260.

Morris, R. G. M. (2013). NMDA receptors and memory encoding. *Neuropharmacology*, **74**, 32–40.

Moscovitch, M. (1995). Confabulation. In D. Schacter (ed.), *Memory distortions: How minds, brains, and societies reconstruct the past* (pp. 226–251). Cambridge, MA: Harvard University Press.

Moscovitch, M., Westmacott, R., Gilboa, A., Addis, D. R., Rosenbaum, R. S., Viskontas, I., et al. (2005). Hippocampal complex contributions to retention and retrieval of recent and remote episodic and semantic memories: Evidence from behavioural and neuroimaging studies of normal and brain-damaged people. In N. Ohta, C. M. MacLeod, and B. Utzl (eds.), *Dynamic cognitive processes* (pp. 333–380). Tokyo:

Springer-Verlag.

Moser, M.-B., Rowland, D. C., and Moser, E. I. (2015). Place cells, grid cells, and memory. *Cold Spring Harbor Perspectives in Biology*, **7**(2), a021808.

<http://doi.org/10.1101/cshperspect.a021808>

Mullally, S. L., and Maguire, E. A. (2014). Memory, imagination, and predicting the future: A common brain mechanism? *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, **20**(3), 220–234.

Müller, N. G., and Knight, R. T. (2006). The functional neuroanatomy of working memory: Contributions of human brain lesion studies. *Neuroscience*, **139**(1), 51–58.

Muller, R. U., Kubie, J. L., and Ranck, J. B. (1987). Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *Journal of Neuroscience*, **7**(7), 1935–1950.

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology*, **7**, 217–227.

Norman, K. A. (2010). How hippocampus and cortex contribute to recognition memory: Revisiting the complementary learning systems model. *Hippocampus*, **20**(11), 1217–1227.

Noulhaine, M., Piolino, P., Hasboun, D., Clemenceau, S., Baulac, M., and Samson, S. (2007). Autobiographical memory after temporal lobe resection: Neuropsychological and MRI volumetric findings. *Brain*, **130**(12), 3184.

Nudo, R. J., Milliken, G. W., Jenkins, W. M., and Merzenich, M. M. (1996). Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, **16**(2), 785–807.

Nyberg, L., Habib, R., McIntosh, A. R., and Tulving, E. (2000). Reactivation of

encoding-related brain activity during memory retrieval. *Proceedings of the National Academy of Sciences*, **97**(20), 11120–11124.

O'Keefe, J., and Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature*, **381**(6581), 425–428.

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, **34**(1), 171–175.

O'Reilly, R. C., and Norman, K. A. (2002). Hippocampal and neocortical contributions to memory: Advances in the complementary learning systems framework. *Trends in Cognitive Sciences*, **6**, 505–510.

O'Reilly, R. C., and Rudy, J. W. (2001). Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. *Psychological Review*, **108**(2), 311–345.

Packard, M., and Knowlton, B. (2002). Learning and memory functions of the basal ganglia. *Annual Review in Neuroscience*, **25**, 563–593.

Packard, M. G., and McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory*, **65**(1), 65–72.

Paller, K. A., Kutas, M., and Mayes, R. A. R. (1987). Neural correlates of encoding in an incidental learning paradigm. *Electroencephalography and Clinical Neurophysiology*, **67**(4), 360–371.

Paniak, C., MacDonald, J., Toller-Lobe, G., Durand, A., and Nagy, J. (1998). A preliminary normative profile of mild traumatic brain injury diagnostic criteria. *Journal of Clinical and Experimental Neuropsychology*, **20**(6), 852–855.

Patterson, K., Nestor, P. J., and Rogers, T. T. (2007). Where do you know what you

know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, **8**(12), 976–987.

Pavlidis, C., and Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *Journal of Neuroscience*, **9**(8), 2907–2918.

Phelps, E. A., Delgado, M. R., Nearing, K. I., and LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, **43**, 897–905.

Phelps, E. A., and LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, **48**(2), 175–187.

Plihal, W., and Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, **9**, 534–547.

Plihal, W., and Born, J. (1999). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology*, **36**, 571–582.

Pobric, G., Jefferies, E., and Ralph, M. A. L. (2007). Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants. *Proceedings of the National Academy of Sciences*, **104**(50), 20137–20141. <http://doi.org/10.1073/pnas.0707383104>

Poldrack, R. A., and Gabrieli, J. D. (2001). Characterizing the neural mechanisms of skill learning and repetition priming: Evidence from mirror reading. *Brain*, **124**(Pt. 1), 67–82.

Poldrack, R. A., and Packard, M. (2003). Competition among multiple memory systems: Converging evidence from animal and human brain studies. *Neuropsychologia*, **41**, 245–251.

Poldrack, R. A., Prabhakaran, V., Seger, C. A., and Gabrieli, J. D. E. (1999). Striatal

activation during acquisition of a cognitive skill. *Neuropsychology*, **13**, 564–574.

Polyn, S. M., Natu, V. S., Cohen, J. D., and Norman, K. A. (2005). Category-specific cortical activity precedes retrieval during memory search. *Science*, **310**(5756), 1963–1966.

Postle, B. R., Druzgal, T. J., and D'Esposito, M. (2003). Seeking the neural substrates of visual working memory storage. *Cortex*, **39**, 927–946.

Ranganath, C., and Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, **13**(10), 713–726.

Rasch, B., Bickel, C., Gais, S., and Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science*, **315**(5817), 1426–1429.

Raymond, C. R. (2007). LTP forms 1, 2 and 3: Different mechanisms for the “long” in long-term potentiation. *Trends in Neurosciences*, **30**, 167–175.

Recanzone, G. H., Merzenich, M. M., and Jenkins, W. M. (1992). Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. *Journal of Neurophysiology*, **67**(5), 1071–1091.

Recanzone, G. H., Schreiner, C. E., and Merzenich, M. M. (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience*, **13**(1), 87–103.

Reder, L. M., Park, H., and Kieffaber, P. D. (2009). Memory systems do not divide on consciousness: Reinterpreting memory in terms of activation and binding. *Psychological Bulletin*, **135**, 23–49.

Reed, J. M., and Squire, L. R. (1998). Retrograde amnesia for facts and events: Findings from four new cases. *Journal of Neuroscience*, **18**(10), 3943–3954.

Repov, G., and Baddeley, A. D. (2006). The multi-component model of working memory: Explorations in experimental cognitive psychology. *Neuroscience*, **139**, 5–21.

Ribot, T. (1881/1882). *Diseases of memory*. New York: Appleton.

Rice, G. E., Hoffman, P., and Lambon Ralph, M. A. (2015). Graded specialization within and between the anterior temporal lobes. *Annals of the New York Academy of Sciences*, **1359**(1), 84–97.

Rosenbaum, R. S., Gilboa, A., and Moscovitch, M. (2014). Case studies continue to illuminate the cognitive neuroscience of memory. *Annals of the New York Academy of Sciences*, **1316**(1), 105–133.

Rugg, M. D., and Curran, T. (2007). Event-related potentials and recognition memory. *Trends in Cognitive Sciences*, **11**, 251–257.

Ruitenbergh, M. F. L., Duthoo, W., Santens, P., Notebaert, W., and Abrahamse, E. L. (2015). Sequential movement skill in Parkinson's disease: A state-of-the-art. *Cortex*, **65**, 102–112.

Ryan, J. D., Althoff, R. R., Whitlow, S., and Cohen, N. J. (2000). Amnesia is a deficit in relational memory. *Psychological Science*, **11**(6), 454–461.

Ryan, L., Cox, C., Hayes, S. M., and Nadel, L. (2008). Hippocampal activation during episodic and semantic memory retrieval: Comparing category production and category cued recall. *Neuropsychologia*, **46**, 2109–2121.

Sadeh, T., Ozubko, J. D., Winocur, G., and Moscovitch, M. (2014). How we forget may depend on how we remember. *Trends in Cognitive Sciences*, **18**(1), 26–36.

Sadeh, T., Ozubko, J. D., Winocur, G., and Moscovitch, M. (2016). Forgetting patterns differentiate between two forms of memory representation. *Psychological Science*, **27**(6), 810–820.

Sadek, J. R., Johnson, S. A., White, D. A., Salmon, D. P., Taylor, K. I., Delapena, J. H., et al. (2004). Retrograde amnesia in dementia: Comparison of HIV-associated dementia, Alzheimer's disease, and Huntington's disease. *Neuropsychology*, **18**(4), 692–699.

Sanders, A. L., Wheeler, M. E., and Buckner, R. L. (2000). Episodic recognition modulates frontal and parietal cortex activity. *Journal of Cognitive Neuroscience*, (Suppl.) **50A**.

Sandrini, M., Rossini, P., and Miniussi, C. (2008). Lateralized contribution of prefrontal cortex in controlling task-irrelevant information during verbal and spatial working memory tasks: rTMS evidence. *Neuropsychologia*, **46**(7), 2056–2063.

Schacter, D. L. (1987). Implicit memory: History and current status. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **13**, 501–518.

Schacter, D. L., and Addis, D. R. (2009). On the nature of medial temporal lobe contributions to the constructive simulation of future events. *Philosophical Transactions of the Royal Society of London, Series B*, **364**(1521), 1245–1253.

Schacter, D. L., Curran, T., Galluccio, L., Milberg, W. P., and Bates, J. F. (1996). False recognition and the right frontal lobe: A case study. *Neuropsychologia*, **34**(8), 793–808.

Schreiner, T., and Rasch, B. (2017). The beneficial role of memory reactivation for language learning during sleep: A review. *Brain and Language*, **67**, 94–105.

Schultz, W., Dayan, P., and Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, **275**(5306), 1593–1599.

Scoville, W. B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, **20**, 11–15.

Seitz, R. J., and Roland, E. (1992). Learning of sequential finger movements in man: A

combined kinematic and positron emission tomography (PET) study. *European Journal of Neuroscience*, **4**, 154–165.

Sestieri, C., Shulman, G. L., and Corbetta, M. (2017). The contribution of the human posterior parietal cortex to episodic memory. *Nature Reviews Neuroscience*, **18**(3), 183–192.

Shallice, T., and Warrington, E. K. (1970). Independent functioning of verbal memory stores: A neuropsychological study. *Quarterly Journal of Experimental Psychology*, **22**, 261–273.

Shallice, T., and Warrington, E. K. (1979). Auditory-verbal short-term memory impairment and conduction aphasia. *Brain and Language*, **4**, 479–491.

Shapiro, M. L., Heikki, T., and Eichenbaum, H. (1997). Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. *Hippocampus*, **7**(6), 624–642.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. A., and Poldrack, R. A. (2004). Cortico-striatal contributions to feedback-based learning: Converging data from neuroimaging and neuropsychology. *Brain*, **127**, 851–859.

Simons, J. S., Peers, P. V., Mazuz, Y. S., Berryhill, M. E., and Olson, I. R. (2010). Dissociation between memory accuracy and memory confidence following bilateral parietal lesions. *Cerebral Cortex*, **20**, 479–485.

Simmons, W. K., and Martin, A. (2009). The anterior temporal lobes and the functional architecture of semantic memory. *Journal of the International Neuropsychological Society*, **15**(5), 645–649.

Skaggs, W. E., and McNaughton, B. L. (1996). Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*, **271**(5257), 1870–1873.

Skinner, E. I., and Fernandes, M. A. (2007). Neural correlates of recollection and familiarity: A review of neuroimaging and patient data. *Neuropsychologia*, **45**, 2163–2179.

Skotko, B. G., Kensinger, E. A., Locascio, J. J., Einstein, G., Rubin, D. C., Tupler, L. A., et al. (2004). Puzzling thoughts for H. M.: Can new semantic information be anchored to old semantic memories? *Neuropsychology*, **18**(4), 756–769.

Smith, C. J., Johnson, B. N., Elkind, J. A., See, J. M., Xiong, G., and Cohen, A. S. (2012). Investigations on alterations of hippocampal circuit function following mild traumatic brain injury. *Journal of Visualized Experiments*, **69**, 4411.

Smith, C. N., and Squire, L. R. (2008). Experience-dependent eye movements reflect hippocampus-dependent (aware) memory. *Journal of Neuroscience*, **28**, 12825–12833.

Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., and Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia*, **47**(8–9), 1765–1779.

Squire, L. R. (2006). Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learning and Memory* (Cold Spring Harbor, NY), **13**(5), 522–529.

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron*, **61**, 6–9.

Squire, L. R., and Bayley, P. J. (2007). The neuroscience of remote memory. *Current Opinion in Neurobiology*, **17**, 185–196.

Squire, L. R., and Cohen, N. J. (1979). Memory and amnesia: Resistance to disruption develops for years after learning. *Behavioral and Neural Biology*, **25**, 115–125.

Squire, L. R., Genzel, L., Wixted, J. T., and Morris, R. G. (2015). Memory consolidation. *Cold Spring Harbor Perspectives in Biology*, **7**(8), a021766.

Squire, L. R., Stark, C. E., and Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, **27**, 279–306.

Sreenivasan, K. K., Curtis, C. E., and D'Esposito, M. (2014). Revisiting the role of persistent neural activity during working memory. *Trends in Cognitive Sciences*, **18**(2), 82–89. <http://doi.org/10.1016/j.tics.2013.12.001>

Staresina, B. P., Cooper, E., and Henson, R. N. (2013). Reversible information flow across the medial temporal lobe: The hippocampus links cortical modules during memory retrieval. *The Journal of Neuroscience*, **33**(35), 14184–14192.

Staresina, B. P., and Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *Journal of Cognitive Neuroscience*, **20**(8), 1478–1489.

Stickgold, R. (2009). The simplest way to reboot your brain. *Harvard Business Review*, **87**, 36.

Stickgold, R. (2013). Parsing the role of sleep in memory processing. *Current Opinion in Neurobiology*, **23**(5), 847–853. <http://doi.org/10.1016/j.conb.2013.04.002>

Steinvorth, S., Levine, B., and Corkin, S. (2005). Medial temporal lobe structures are needed to re-experience remote autobiographical memories: Evidence from H.M. and W.R. *Neuropsychologia*, **43**, 470–496.

Suthana, N. A., Parikshak, N. N., Ekstrom, A. D., Ison, M. J., Knowlton, B. J., Bookheimer, S. Y., and Fried, I. (2015). Specific responses of human hippocampal neurons are associated with better memory. *Proceedings of the National Academy of Sciences*, **112**(33), 10503–10508.

Sutherland, R. J., Whishaw, I. Q., and Kolb, B. (1983). A behavioral analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the

hippocampal formation in the rat. *Behavioral Brain Research*, **7**, 133–153.

Suzuki, W. A., and Naya, Y. (2014). The perirhinal cortex. *Annual Review of Neuroscience*, **37**, 39–53.

Talamini, L. M., Nieuwenhuis, I. L., Takashima, A., and Jensen, O. (2008). Sleep directly following learning benefits consolidation of spatial associative memory. *Learning and Memory*, **15**, 233–237.

Thomas-Antérion, C., Koenig, O., Navez, M., and Laurent, B. (1999). Midazolam effects on implicit and explicit memory processes in healthy subjects. *Psychopharmacology*, **145**, 139–143.

Tulving, E. (1972). Episodic and semantic memory. In E. Tulving and W. Donaldson (eds.), *Organization of memory* (pp. 381–403). New York: Academic Press.

Tulving, E. (1985). Memory and consciousness. *Canadian Psychologist*, **25**, 1–12.

Tyler, T. J., and DiScenna, P. (1986). The hippocampus memory indexing theory. *Behavioral Neuroscience*, **100**, 147–152.

Vallar, G., and Baddeley, A. (1984). Phonological short-term store, phonological processing, and sentence comprehension: A neuropsychological case study. *Cognitive Neuropsychology*, **1**, 121–141.

Vann, S. D., Aggleton, J. P., and Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience*, **10**(11), 792–802.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., van Paesschen, W., and Mishkin, M. (1997). Different effects of early hippocampal pathology on episodic and semantic memory. *Science*, **277**, 376–380.

Vilberg, K. L., and Rugg, M. D. (2008). Memory retrieval and the parietal cortex: A

review of evidence from a dual-process perspective. *Neuropsychologia*, **46**(7), 1787–1799.

Wager, T., and Smith, E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective and Behavioral Neuroscience*, **3**, 255–274.

Wagner, A. D., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. (1998). Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. *Brain*, **121**(10), 1985–2002.

Wagner, A. D., Shannon, B. J., Kahn, I., and Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Science*, **9**, 445–453.

Wheeler, M. A., Stuss, D. T., and Tulving, E. (1995). Frontal lobe damage produces episodic memory impairment. *Journal of the International Neuropsychological Society*, **1**(6), 525–536.

Wheeler, M. E., Petersen, S. E., and Buckner, R. L. (2000). Memory's echo: Vivid remembering reactivates sensory-specific cortex. *Proceedings of the National Academy of Science of the United States of America*, **97**(20), 11125–11129.

Wigstrom, H., and Gustafsson, B. (1985). On long-lasting potentiation in the hippocampus: A proposed mechanism for its dependence on pre- and postsynaptic activity. *Acta Psychologica Scandinavica*, **123**, 519–522.

Wilson, M. A., and McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science*, **265**(5172), 676–679.

Winocur, G., and Moscovitch, M. (2011). Memory transformation and systems consolidation. *Journal of the International Neuropsychological Society*, **17**(5), 766–780.

Wixted, J., and Squire, L. R. (2011). The medial temporal lobe and attributes of memory. *Trends Cogn. Sci.* **15**:210–17.

Yassa, M. A., and Stark, C. E. L. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences*, **34**(10), 515–525.

Yonelinas, A. P. (2001). Components of episodic memory: The contribution of recollection and familiarity. *Philosophical Transactions of the Royal Society of London, Series B***356**, 1363–1374.

Yonelinas, A. P., Aly, M., Wang, W.-C., and Koen, J. D. (2010). Recollection and familiarity: Examining controversial assumptions and new directions. *Hippocampus*, **20**(11), 1178–1194.

Zola-Morgan, S., and Squire, L. R. (1985). Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. *Behavioral Neuroscience*, **99**, 22–34.

Chapter 10

Adair, J. C., and Barrett, A. M. (2008). Spatial neglect: Clinical and neuroscience review: A wealth of information on the poverty of spatial attention. *Annals of the New York Academy of Sciences*, **1142**, 21–43.

Alavash, M., Hilgetag, C. C., Thiel, C. M., and Gießing, C. (2015). Persistency and flexibility of complex brain networks underlie dual-task interference. *Human Brain Mapping*, **36**(9), 3542–3562.

Alavash, M., Thiel, C. M., and Gießing, C. (2016). Dynamic coupling of complex brain networks and dual-task behavior. *NeuroImage*, **129**, 233–246.

<http://doi.org/10.1016/j.neuroimage.2016.01.028>

Anderson, E. J., and Rees, G. (2011). Neural correlates of spatial orienting in the human superior colliculus. *Journal of Neurophysiology*, **106**(5), 2273–2284.

Andrews-Hanna, J. R., Smallwood, J., and Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, **1316**, 29–52.

<http://doi.org/10.1111/nyas.12360>

Anilo-Vento, L., Luck, S. J., and Hillyard, S. A. (1998). Spatiotemporal dynamics of attention to color: Evidence from human electrophysiology. *Human Brain Mapping*, **6**, 216–238.

Arruda, J. E., Walker, K. A., Weiler, M. D., and Valentino, D. A. (1999). Validation of a right hemisphere vigilance system as measured by principal component and factor analyzed quantitative electroencephalogram. *International Journal of Psychophysiology*, **32**, 119–128.

Ashbridge, E., Walsh, V., and Cowey, A. (1997). Temporal aspects of visual search

studies by transcranial magnetic stimulation. *Neuropsychologia*, **35**, 1121–1131.

Baker, J. L., Ryou, J.-W., Wei, X. F., Butson, C. R., Schiff, N. D., and Purpura, K. P. (2016). Robust modulation of arousal regulation, performance, and frontostriatal activity through central thalamic deep brain stimulation in healthy nonhuman primates. *Journal of Neurophysiology*, **116**(5), 2383–2404.

Baldauf, D., and Desimone, R. (2014). Neural mechanisms of object-based attention. *Science*, **344**(6182), 424–427. <http://doi.org/10.1126/science.1247003>

Bartolomeo, P. (2007). Visual neglect. *Current Opinions in Neurology*, **20**, 381–386.

Baylis, G. C., Baylis, L. L., and Gore, C. L. (2004). Visual neglect can be object-based or scene-based depending on task representation. *Cortex*, **40**, 237–246.

Beck, D. M., and Kastner, S. (2014). Neural systems for spatial attention in the human brain. In A. C. K. Nobre and S. Kastner (eds.), *Oxford handbook of attention* (Vol. I, pp. 1–47). Oxford University Press.

Becker, E., and Karnath, H.-O. (2007). Incidence of visual extinction after left versus right hemisphere stroke. *Stroke*, **38**(12), 3172–3174.

Behrmann, M., and Moscovitch, M. (1994). Object-centered neglect in patients with unilateral neglect. *Journal of Cognitive Neuroscience*, **6**, 1–16.

Berridge, C. W., Schmeichel, B. E., and España, R. A. (2012). Noradrenergic modulation of wakefulness/arousal. *Sleep Medicine Reviews*, **16**(2), 187–197.

Berti, A., and Rizzolatti, G. (1992). Visual processing without awareness: Evidence from unilateral neglect. *Journal of Cognitive Neuroscience*, **4**, 345–351.

Bisiach, E., Geminiani, G., Berti, A., and Rusconi, M. L. (1990). Perceptual and premotor factors of unilateral neglect. *Neurology*, **40**, 1278–1281.

Bisiach, E., and Luzzatti, C. (1978). Unilateral neglect of representational space. *Cortex*, **14**, 129–133.

Bisiach, E., Neppi-Modona, M., and Ricci, R. (2002). Space anisometry in unilateral neglect. In H. O. Karnath, A. D. Milner, and G. Villar (eds.), *The cognitive and neural bases of spatial neglect* (pp. 145–152). Oxford: Oxford University Press.

Bisiach, E., and Rusconi, M. L. (1990). Breakdown of perceptual awareness in unilateral neglect. *Cortex*, **24**, 643–649.

Bonato, M., Priftis, K., Marenzi, R., and Zorzi, M. (2008). Modulation of hemispatial neglect by directional and numerical cues in the line bisection task. *Neuropsychologia*, **46**(2), 426–433. <http://doi.org/10.1016/j.neuropsychologia.2007.08.019>

Bowyer, S. M., Hsieh, L., Moran, J. E., Young, R. A., Manoharan, A., Liao, C. C., et al. (2009). Conversation effects on neural mechanisms underlying reaction time to visual events while viewing a driving scene using MEG. *Brain Research*, **1251**, 151–161.

Brighina, F., Bisiach, E., Oliveri, M., Piazza, A., La Bua, V., Daniele, O., and Fierro, B. (2003). 1 Hz repetitive transcranial magnetic stimulation of the unaffected hemisphere ameliorates contralesional visuospatial neglect in humans. *Neuroscience Letters*, **336**, 131–133.

Broadbent, D. E. (1958). *Perception and communication*. London: Pergamon Press.

Caramazza, A., and Hillis, A. (1990). Spatial representation of words in the brain implied by studies of a unilateral neglect patient. *Nature*, **346**, 267–269.

Casali, A. G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K. R., et al. (2013). A theoretically based index of consciousness independent of sensory processing and behavior. *Science Translational Medicine*, **5**(198), 198ra105. <http://doi.org/10.1126/scitranslmed.3006294>

Ciçek, M., Gitelman, D., Hurley, R. S., Nobre, A., and Mesulam, M. (2007). Anatomical physiology of spatial extinction. *Cerebral Cortex*, **17**, 2892–2898.

Cohen, J. C., Braver, T. S., and O'Reilly, R. C. (1996). A computational approach to prefrontal cortex, cognitive control, and schizophrenia: Recent developments and current challenges. *Philosophical Transactions of the Royal Society of London, Series B*, **351**, 1515–1527.

Cohen, M. X., Ridderinkhof, K. R., Haupt, S., Elger, C. E., and Fell, J. (2008). Medial frontal cortex and response conflict: Evidence from human intracranial EEG and medial frontal cortex lesion. *Brain Research*, **1238**, 127–142.

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, **3**(3), 201–215.

Corbetta, M., and Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience*, **34**, 569–599. <http://doi.org/10.1146/annurev-neuro-061010-113731>

Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L., and Petersen, S. E. (1991). Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. *Journal of Neuroscience*, **11**, 2383–2402.

Corbetta, M., Miezin, F. M., Shulman, G. L., and Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience*, **13**, 1202–1226.

Corbetta, M., Patel, G., and Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron*, **58**(3), 306–324. <http://doi.org/10.1016/j.neuron.2008.04.017>

Coslett, H. B., Bowers, D., and Heilman, K. M. (1987). Reduction in cerebral

activation after right hemisphere stroke. *Neurology*, **37**, 957–962.

Coull, J. T., and Nobre, A. C. (1998). Where and when to pay attention: The neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *Journal of Neuroscience*, **18**, 7426–7435.

Coull, J. T., Nobre, A. C., and Frith, C. D. (2001). The noradrenergic alpha-2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. *Cerebral Cortex*, **11**, 73–84.

Damasio, A. R., Damasio, H., and Chui, H. C. (1980). Neglect following damage to frontal lobe or basal ganglia. *Neuropsychologia*, **18**, 123–132.

Dambeck, N., Sparing, R., Meister, I. G., Wienemann, M., Weidemann, J., Topper, R., and Boroojerdi, B. (2006). Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Research*, **1072**, 194–199.

Desimone, R., and Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, **18**, 193–222.

Desimone, R., Wessinger, M., Thomas, L., and Schneider, W. (1990). Attentional control of visual perception: Cortical and subcortical mechanisms. *Cold Spring Harbor Symposia on Quantitative Biology*, **55**, 963–971.

Desmedt, J. E., and Robertson, D. (1977). Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during forced-paced cognitive tasks in man. *Journal of Physiology (London)*, **271**, 761–782.

Deutsch, J. A., and Deutsch, D. (1963). Attention: Some theoretical considerations. *Psychological Review*, **70**, 80–90.

Di Russo, F., Aprile, T., Spitoni, G., and Spinelli, D. (2008). Impaired visual

processing of contralesional stimuli in neglect patients: A visual-evoked potential study. *Brain*, **131**, 842–854.

Doesburg, S. M., Bedo, N., and Ward, L. M. (2016). Top-down alpha oscillatory network interactions during visuospatial attention orienting. *NeuroImage*, **132**, 512–519.

Donchin, E. (1981). Surprise! ... Surprise? *Psychophysiology*, **18**, 493–513.

Downing, P., Liu, J., and Kanwisher, N. (2001). Testing cognitive models of visual attention with fMRI and MEG. *Neuropsychologia*, **39**, 1329–1342.

Driver, J., Baylis, G., Goodrich, S. J., and Rafal, R. D. (1994). Axis-based neglect of visual shapes. *Neuropsychologia*, **32**, 1353–1365.

Driver, J., and Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition*, **79**, 39–88.

Dux, P. E., Ivanoff, J., Asplund, C. L., and Marois, R. (2006). Isolation of a central bottleneck of information processing with time-resolved FMRI. *Neuron*, **52**(6), 1109–1120.

Dux, P. E., Tombu, M. N., Harrison, S., Rogers, B. P., Tong, F., and Marois, R. (2009). Training improves multitasking performance by increasing the speed of information processing in human prefrontal cortex. *Neuron*, **63**(1), 127–138.

Edlow, B. L., Takahashi, E., Wu, O., Benner, T., Dai, G., Bu, L., et al. (2012). Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders. *Journal of Neuropathology and Experimental Neurology*, **71**(6), 531–546. <http://doi.org/10.1097/NEN.0b013e3182588293>

Eimer, M. (2014). The time course of spatial attention. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 289–317). Oxford: Oxford University Press.

Fairhall, S. L., and Macaluso, E. (2009). Spatial attention can modulate audiovisual integration at multiple cortical and subcortical sites. *European Journal of Neuroscience*, **29**, 1247–1257.

Fan, J., Gu, X., Guise, K. G., Liu, X., Fossella, J., Wang, H., and Posner, M. I. (2009). Testing the behavioral interaction and integration of attentional networks. *Brain and Cognition*, **70**, 209–220.

Fasotti, L., and van Kessel, M. (2013). Novel insights in the rehabilitation of neglect. *Frontiers in Human Neuroscience*, **7**, 780.

Fink, G. R., Dolan, R. J., Halligan, P. W., Marshall, J. C., and Frith, C. D. (1997). Space-based and object-based visual attention: Shared and specific neural domains. *Brain*, **120**, 2013–2028.

Fox, M., Snyder, A. Z., Vincent, J. L., Corbetta, M., van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, **102**, 9673–9678.

Frassinetti, F., Rossi, M., and Ládavas, E. (2001). Passive limb movements improve visual neglect. *Neuropsychologia*, **39**, 725–733.

Friedman-Hill, S. R., Robertson, L. C., and Treisman, A. M. (1995). Parietal contributions to visual feature binding: Evidence from a patient with bilateral lesions. *Science*, **269**, 853–855.

Gottlieb, J. (2014). Neuronal mechanisms of attentional control. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 346–374). Oxford: Oxford University Press.

Gottlieb, J., Balan, P., Oristaglio, J., and Suzuki, M. (2009). Parietal control of

attentional guidance: The significance of sensory, motivational and motor factors. *Neurobiology of Learning and Memory*, **91**, 121–128.

Gregoriou, G. G., Gotts, S. J., Zhou, H., and Desimone, R. (2009). High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science*, **324**(5931), 1207–1210.

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., and Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nature Neuroscience*, **17**(7), 1003–1011. <http://doi.org/10.1038/nn.3742>

Guittou, D., Buchtel, H. A., and Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research*, **58**, 455–472.

Hahn, B., Wolkenberg, F. A., Ross, T. J., Myers, C. S., Heishman, S. J., Stein, D. J., et al. (2008). Divided versus selective attention: Evidence for common processing mechanisms. *Brain Research*, **1215**, 137–146.

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Munte, T. F., et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature*, **372**, 543–546.

Heinze, H. J., Luck, S. J., Mangun, G. R., and Hillyard, S. A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays: 1. Evidence for early selection. *Electroencephalography and Clinical Neurophysiology*, **75**(6), 511–527.

Hendrickson, R. C., and Raskind, M. A. (2016). Noradrenergic dysregulation in the pathophysiology of PTSD. *Experimental Neurology*, **284**, 181–195. <http://doi.org/10.1016/j.expneurol.2016.05.014>

Herd, S. A., Banich, M. T., and O'Reilly, R. C. (2006). Neural mechanisms of cognitive

control: An integrative model of Stroop task performance and fMRI data. *Journal of Cognitive Neuroscience*, **18**, 22–32.

Hillis, A. E., and Caramazza, A. (1991). Deficit to stimulus-centered, letter shape representations in a case of “unilateral neglect.” *Neuropsychologia*, **29**(12), 1223–1240.

Hillyard, S. A., Hink, R. F., Schwent, V. L., and Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science*, **182**, 177–180.

Howes, D., and Boller, F. (1975). Simple reaction time: Evidence for focal impairment from lesions of the right hemisphere. *Brain*, **98**, 317–332.

Husain, M., and Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience*, **4**, 26–36.

Ishigami, Y., and Klein, R. M. (2009). Is a hands-free phone safer than a handheld phone? *Journal of Safety Research*, **40**(2), 157–164.

<http://doi.org/10.1016/j.jsr.2009.02.006>

Isomura, Y., Ito, Y., Akazawa, T., Nambu, A., and Takada, M. (2003). Neural coding of “attention for action” and “response selection” in primate anterior cingulate cortex. *Journal of Neuroscience*, **23**, 8003–8012.

Jacobs, S., Brozzoli, C., and Farnè, A. (2012). Neglect: A multisensory deficit? *Neuropsychologia*, **50**(6), 1029–1044.

<http://doi.org/10.1016/j.neuropsychologia.2012.03.018>

Jacquin-Courtois, S. (2015). Hemi-spatial neglect rehabilitation using non-invasive brain stimulation: Or how to modulate the disconnection syndrome? *Annals of Physical and Rehabilitation Medicine*, **58**(4), 251–258.

Johannsen, L., Ackermann, H., and Karnath, H. O. (2003). Lasting amelioration of

spatial neglect by treatment with neck muscle vibration even without concurrent training. *Journal of Rehabilitation Medicine*, **35**, 249–253.

Johnson, J. A., Strafella, A. P., and Zatorre, R. J. (2007). The role of the dorsolateral prefrontal cortex in bimodal divided attention: Two transcranial magnetic stimulation studies. *Journal of Cognitive Neuroscience*, **19**, 907–920.

Johnson, J. A., and Zatorre, R. J. (2006). Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. *NeuroImage*, **31**, 1673–1681.

Jones, B. E. (2003). Arousal systems. *Frontiers in Bioscience*, **8**, s438–s451.

Just, M. A., Keller, T. A., and Cynkar, J. (2008). A decrease in brain activation associated with driving while listening to someone speak. *Brain Research*, **1205**, 70–80.

Kahneman, D. (1973). *Attention and effort*. Englewood Cliffs, NJ: Prentice Hall.

Karnath, H.-O., and Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia*, **50**(6), 1010–1017.
<http://doi.org/10.1016/j.neuropsychologia.2011.06.027>

Kastner, S., de Weerd, P., Desimone, R., and Ungerleider, L. G. (1998). Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science*, **282**, 108–111.

Kastner, S., and Pisk, M. A. (2004). Visual attention as a multilevel selection process. *Cognitive, Affective, and Behavioral Neuroscience*, **4**, 483–500.

Kastner, S., Pisk, M. A., de Weerd, P., Desimone, R., and Ungerleider, L. G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron*, **22**, 751–761.

Kelley, T. A., Serences, J. T., Giesbrecht, B., and Yantis, S. (2008). Cortical mechanisms for shifting and holding visuospatial attention. *Cerebral Cortex*, **18**, 114–125.

Kerkhoff, G., Keller, I., Artinger, F., Hildebrandt, H., Marquardt, C., Reinhart, S., and Ziegler, W. (2012). Recovery from auditory and visual neglect after optokinetic stimulation with pursuit eye movements—transient modulation and enduring treatment effects. *Neuropsychologia*, **50**(6), 1164–1177.

<http://doi.org/10.1016/j.neuropsychologia.2011.09.032>

Kerkhoff, G., Keller, I., Ritter, V., and Marquardt, C. (2006). Repetitive optokinetic stimulation induces lasting recovery from visual neglect. *Restorative Neurology and Neuroscience*, **24**, 357–369.

Kerkhoff, G., and Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia*, **50**(6), 1072–1079.

<http://doi.org/10.1016/j.neuropsychologia.2012.01.024>

Kim, Y. K., Jung, J. H., and Shin, S. H. (2015). A comparison of the effects of repetitive transcranial magnetic stimulation (rTMS) by number of stimulation sessions on hemispatial neglect in chronic stroke patients. *Experimental Brain Research*, **233**(1), 283–289. <http://doi.org/10.1007/s00221-014-4112-9>

Kim, Y.-H., Min, S.-J., Ko, M.-H., Park, J.-W., Jang, S. H., and Lee, P. K. W. (2005). Facilitating visuospatial attention for the contralateral hemifield by repetitive TMS on the posterior parietal cortex. *Neuroscience Letters*, **382**, 280–285.

Kinsbourne, M. (1970). A model for the mechanism of unilateral neglect of space. *Transactions of the American Neurological Association*, **95**, 143–145.

Kinsbourne, M. (1974). Lateral interaction in the brain. In M. Kinsbourne and W. L. Smith (eds.), *Hemispheric disconnections and cerebral function* (pp. 239–259).

Springfield, IL: Charles C. Thomas.

Kinsbourne, M. (1987). Mechanisms of unilateral neglect. In M. Jeannerod (ed.), *Neurophysiological and neuropsychological aspects of spatial neglect* (pp. 69–83). Amsterdam: Elsevier.

Kinsbourne, M. (1993). Orientational bias model of unilateral neglect: Evidence from attentional gradients within hemispace. In I. H. Robertson and J. C. Marshall (eds.), *Unilateral neglect: Clinical and experimental studies*. Hillsdale, NJ: Erlbaum.

Klimesch, W., Sauseng, P., Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition timing hypothesis. *Brain Research Reviews*, **53**(1), 63–88.

Knight, R. T., Scabini, D., Woods, D. L., and Clayworth, C. C. (1989). Contribution of temporal-parietal junction to the human auditory P3. *Brain Research*, **502**, 109–116.

Koch, C., Massimini, M., Boly, M., and Tononi, G. (2016). Neural correlates of consciousness: Progress and problems. *Nature Reviews Neuroscience*, **17**(5), 307–321.
<http://doi.org/10.1038/nrn.2016.22>

Kramer, A. F., Wickens, C. D., and Donchin, E. (1985). Processing of stimulus properties: Evidence for dual-task integrality. *Journal of Experimental Psychology: Human Perception and Performance*, **11**(4), 393–408.

Krauzlis, R. J. (2014). Attentional functions of the superior colliculus. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 423–445). Oxford: Oxford University Press.

Lavie, N. (1995). Perceptual load as a necessary condition for selective attention. *Journal of Experimental Psychology: Human Perception and Performance*, **21**, 451–468.

Lavie, N., and Dalton, P. (2014). Load theory of attention and cognitive control. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 56–75).

Oxford: Oxford University Press.

Lavie, N., and Tsal, Y. (1994). Perceptual load as a major determinant of the locus of selection in visual attention. *Perception and Psychophysics*, **56**, 183–197.

Leitão, J., Thielscher, A., Tünnerhoff, J., and Noppeney, U. (2015). Concurrent TMS-fMRI reveals interactions between dorsal and ventral attentional systems. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **35**(32), 11445–11457.

Levy, J., Heller, W., Banich, M. T., and Burton, L. A. (1983). Asymmetry of perception in free viewing of chimeric faces. *Brain and Cognition*, **2**, 404–419.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical “alarm” system for subliminal signals of fear. *NeuroImage*, **24**, 235–243.

Liu, X., Banich, M. T., Jacobson, B. L., and Tanabe, J. L. (2006). Functional dissociation of attentional selection within PFC: Response and non-response related aspects of attentional selection as ascertained by fMRI. *Cerebral Cortex*, **16**, 827–834.

Loose, R., Kaufmann, C., Auer, D. P., and Lange, K. W. (2003). Human prefrontal and sensory cortical activity during divided attention tasks. *Human Brain Mapping*, **18**(4), 249–259.

Luck, S. J., and Hillyard, S. A. (1994). Spatial filtering during visual search: Evidence from human electrophysiology. *Journal of Experimental Psychology: Human Perception and Performance*, **20**, 1000–1014.

Luck, S. J., and Kappenman, E. S. (2011). ERP components and selective attention. In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potentials* (pp. 298–328). Oxford: Oxford University Press.

Lunven, M., Thiebaut de Schotten, M., Bourlon, C., Duret, C., Migliaccio, R., Rode, G., and Bartolomeo, P. (2015). White matter lesional predictors of chronic visual neglect: A longitudinal study. *Brain*, **138**(Pt. 3), 746–760.

Malhotra, P., Coulthard, E. J., and Husain, M. (2009). Role of right posterior parietal cortex in maintaining attention to spatial locations over time. *Brain*, **132**, 645–660.

Malhotra, P. A., Soto, D., Li, K., and Russell, C. (2013). Reward modulates spatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry*, **84**(4), 366–369.
<http://doi.org/10.1136/jnmp-2012-303169>

Mangun, G. R., Buonocore, M. H., Girelli, M., and Jha, A. P. (1998). ERP and fMRI measures of visual spatial selection attention. *Human Brain Mapping*, **6**, 383–389.

Mangun, G. R., and Hillyard, S. A. (1988). Spatial gradients of visual attention: Behavioral and electrophysiological evidence. *Electroencephalography and Clinical Neurophysiology*, **70**, 417–428.

Mark, V. W., Kooistra, C. A., and Heilman, K. M. (1988). Hemispatial neglect affected by non-neglected stimuli. *Neurology*, **38**, 1207–1211.

Marshall, J. C., and Halligan, P. W. (1988). Blindsight and insight in visuospatial neglect. *Nature*, **336**, 766–767.

McAlonan, K., Cavanaugh, J., and Wurtz, R. H. (2006). Attentional modulation of thalamic reticular neurons. *Journal of Neuroscience*, **26**, 4444–4450.

McGaughey, J., Kaiser, T., and Sarter, M. (1996). Behavioral vigilance following infusions of 192 IgG-saporin into the basal forebrain: Selectivity of the behavioral impairment and relation to cortical AChE-positive fiber density. *Behavioral Neuroscience*, **110**(2), 247–265.

McGlinchey-Berroth, R., Milberg, W. P., Verfaellie, M., Alexander, M., and Kilduff,

P. T. (1993). Semantic processing in the neglected visual field: Evidence from a lexical decision task. *Cognitive Neuropsychology*, **10**, 79–108.

Medeiros-Ward, N., Watson, J. M., and Strayer, D. L. (2014). On supertaskers and the neural basis of efficient multitasking. *Psychonomic Bulletin and Review*, **22**(3), 876–883.

Meister, I. G., Wienemann, M., Buelte, D., Grünewald, C., Sparing, R., Dambeck, N., and Boroojerdi, B. (2006). Hemiextinction induced by transcranial magnetic stimulation over the right temporo-parietal junction. *Neuroscience*, **142**, 119–123.

Mesulam, M.-M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, **10**, 309–325.

Mesulam, M.-M. (ed.). (1985). *Principles of behavioral neurology*. Philadelphia: F. A. Davis.

Milham, M. P., Banich, M. T., Webb, A., Barad, V., Cohen, N. J., Wszalek, T., and Kramer, A. F. (2001). The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Cognitive Brain Research*, **12**, 467–473.

Milner, A. D., and McIntosh, R. D. (2005). The neurological basis of visual neglect. *Current Opinion in Neurology*, **18**, 748–753.

Molenberghs, P., Cunnington, R., and Mattingley, J. B. (2012a). Brain regions with mirror properties: A meta-analysis of 125 human fMRI studies. *Neuroscience and Biobehavioral Reviews*, **36**(1), 341–349.

Molenberghs, P., Sale, M. V., and Mattingley, J. B. (2012b). Is there a critical lesion site for unilateral spatial neglect? A meta-analysis using activation likelihood estimation. *Frontiers in Human Neuroscience*, **6**, 78, figure 3, page 7.

<http://doi.org/10.3389/fnhum.2012.00078>

Monti, J. M. (2011). Serotonin control of sleep–wake behavior. *Sleep Medicine Reviews*, **15**(4), 269–281. <http://doi.org/10.1016/j.smr.2010.11.003>

Moran, J., and Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. *Science*, **229**, 782–784.

Mozer, M. C., and Sitton, M. (1998). Computational modeling of spatial attention. In H. Pashler (ed.), *Attention* (pp. 341–395). Hove: Psychology Press.

Müsch, K., Hamamé, C. M., Perrone-Bertolotti, M., Minotti, L., Kahane, P., Engel, A. K., et al. (2014). Selective attention modulates high-frequency activity in the face-processing network. *Cortex*, **60**, 34–51. <http://doi.org/10.1016/j.cortex.2014.06.006>

Nebel, K., Wiese, H., Stude, P., de Greiff, A., Diener, H. C., and Keidel, M. (2005). On the neural basis of focused and divided attention. *Cognitive Brain Research*, **25**, 760–776.

Nijboer, M., Borst, J., van Rijn, H., and Taatgen, N. (2014). Single-task fMRI overlap predicts concurrent multitasking interference. *NeuroImage*, **100**, 60–74. <http://doi.org/10.1016/j.neuroimage.2014.05.082>

Nobre, A. C., Gitelman, D. R., Sebestyen, G. N., Meyer, J., Frackowiak, R. S. J., Frith, C. D., and Mesulam, M. M. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain*, **120**, 515–553.

O'Connor, D. H., Fukui, M. M., Pinsk, M. A., and Kastner, S. (2002). Attention modulates responses in the human lateral geniculate nucleus. *Nature Neuroscience*, **5**, 1203–1209.

O'Craven, K., Downing, P., and Kanwisher, N. (1999). fMRI evidence for objects as the units of attentional selection. *Nature*, **401**, 584–587.

Oliveri, M., Bisiach, E., Brighina, F., Piazza, A., La Bua, V., Buffa, D., and Fierro, B. (2001). rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology*, **57**, 1338–1340.

Oliveri, M., and Caltagirone, C. (2006). Suppression of extension with TMS in humans: From healthy controls to patients. *Behavioural Neurology*, **17**, 163–167.

Olk, B., Peschke, C., and Hilgetag, C. C. (2015). Attention and control of manual responses in cognitive conflict: Findings from TMS perturbation studies. *Neuropsychologia*, **74**, 7–20.

O'Reilly, R. C., Munakata, Y., Frank, M. J., Hazy, T. E., and Contributors. (2012). Computational Cognitive Neuroscience. Wiki Book (1st Edn.). URL: <http://ccnbook.colorado.edu>

Ota, H., Fujii, T., Suzuki, K., Fukatsu, R., and Yamadori, A. (2001). Dissociation of body-centered and stimulus-centered representations in unilateral neglect. *Neurology*, **57**, 2064–2069.

Parton, A., Nachev, P., Hodgson, T. L., Mort, D., Thomas, D., Ordidge, R., et al. (2007). Role of the human supplementary eye field in the control of saccadic eye movements. *Neuropsychologia*, **45**(5), 997–1008.

Paus, T., Kalina, M., Patockova, L., Angerova, Y., Cerny, R., Mecir, P., et al. (1991). Medial versus lateral frontal lobe lesions and differential impairment of central-gaze fixation maintenance in man. *Brain*, **114**, 2051–2067.

Paus, T., Zatorre, R. J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., and Evans, A. C. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience*, **9**, 392–408.

Pavani, F., Husain, M., Ládavas, E., and Driver, J. (2004). Auditory deficits in visuospatial neglect patients. *Cortex*, **40**(2), 347–365.

Pavani, F., Ládavas, E., and Driver, J. (2003). Auditory and multisensory aspects of visuospatial neglect. *Trends in Cognitive Sciences*, **7**, 407–414.

Pessoa, L., Kastner, S., and Ungerlieder, L. G. (2003). Neuroimaging studies of attention from modulation of sensory processing to top-down control. *The Journal of Neuroscience*, **10**, figures 1A and 1B, page 3992.

Portas, C. M., Rees, G., Howseman, A. M., Josephs, O., Turner, R., and Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *Journal of Neuroscience*, **18**, 8979–8989.

Posner, M. I., and Rothbart, M. K. (2007). Research on attention networks as a model for the integration of psychological science. *Annual Review of Psychology*, **58**, 1–23.

Posner, M. I., Walker, J. A., Friedrich, F. J., and Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience*, **4**, 1863–1874.

Ptak, R. (2012). The frontoparietal attention network of the human brain: Action, saliency, and a priority map of the environment. *The Neuroscientist*, **18**(5), 502–515.
<http://doi.org/10.1177/1073858411409051>

Rafal, R., and Posner, M. I. (1987). Deficits in human visual spatial attention following thalamic lesions. *Proceedings of the National Academy of Sciences*, **84**, 7349–7353.

Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., and Bernstein, E. (1988). Orienting of visual attention in progressive supranuclear palsy. *Brain*, **111**, 267–280.

Raichle, M. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, **98**, 676–682.

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, **38**, 433–447.

Reddy, L., Kanwisher, N. G., and Vanrullen, R. (2009). Attention and biased competition in multi-voxel object representations. *Proceedings of the National Academy of Sciences*, **106**(50), 21447–21452.

Rees, G., Frith, C. D., and Lavie, N. (1997). Modulating irrelevant motion perception by varying attentional load in an unrelated task. *Science*, **278**, 1616–1619.

Rees, G., Wojciulik, E., Clarke, K., Husain, M., Frith, C., and Driver, J. (2000). Unconscious activation of visual cortex in the damaged right hemisphere of a parietal patient with extinction. *Brain*, **123**, 1624–1633.

Rees, G., Wojciulik, E., Clarke, K., Husain, M., Frith, C., and Driver, J. (2002). Neural correlates of conscious and unconscious vision in parietal extinction. *Neurocase*, **8**, 387–393.

Reuter-Lorenz, P. A., Kinsbourne, M., and Moscovitch, M. (1990). Hemispheric control of spatial attention. *Brain and Cognition*, **12**, 240–266.

Reuter-Lorenz, P. A., and Posner, M. I. (1990). Components of neglect from right-hemisphere damage: An analysis of line bisection. *Neuropsychologia*, **28**, 327–333.

Reynolds, J. H., Chelazzi, L., and Desimone, R. (1999). Competitive mechanisms subserve attention in macaque areas V2 and V4. *Journal of Neuroscience*, **19**, 1736–1753.

Riddoch, M. J., and Humphreys, G. W. (1983). The effect of cueing on unilateral neglect. *Neuropsychologia*, **21**, 589–599.

Rinne, P., Hassan, M., Goniotakis, D., Chohan, K., Sharma, P., Langdon, D., et al. (2013). Triple dissociation of attention networks in stroke according to lesion location.

Neurology, **81**(9), 812–820.

Rorden, C., Hjalton, H., Fillmore, P., Fridriksson, J., Kjartansson, O., Magnusdottir, S., and Karnath, H.-O. (2012). Allocentric neglect strongly associated with egocentric neglect. *Neuropsychologia*, **50**(6), 1151–1157.

<http://doi.org/10.1016/j.neuropsychologia.2012.03.031>

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., and Perenin, M. T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, **395**, 166–169.

Rubens, A. B. (1985). Caloric stimulation and unilateral visual neglect. *Neurology*, **35**, 1019–1024.

Saalmann, Y. B., and Kastner, S. (2014). Neural mechanisms of spatial attention in the visual thalamus. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 399–422). Oxford: Oxford University Press.

Saalmann, Y. B., Pinsk, M. A., Wang, L., Li, X., and Kastner, S. (2012). The pulvinar regulates information transmission between cortical areas based on attention demands. *Science*, **337**(6095), 753–756.

Salo, E., Rinne, T., Salonen, O., and Alho, K. (2015). Brain activations during bimodal dual tasks depend on the nature and combination of component tasks. *Frontiers in Human Neuroscience*, **9**, 102.

Samuelsson, H., Hjelmquist, E., Jensen, C., Ekholm, S., and Blomstrand, C. (1998). Nonlateralized attentional deficits: An important component behind persisting visuospatial neglect? *Journal of Clinical and Experimental Neuropsychology*, **20**, 73–88.

Sanbonmatsu, D. M., Strayer, D. L., Behrends, A. A., Ward, N., and Watson, J. M. (2016). Why drivers use cell phones and support legislation to restrict this practice.

Accident; Analysis and Prevention, **92**, 22–33.

<http://doi.org/10.1016/j.aap.2016.03.010>

Saper, C. B., Chou, T. C., and Scammell, T. E. (2001). The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neurosciences*, **24**(12), 726–731, figure 1, page 727.

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Neuroscience*, **10**, 211–223.

Sarter, M., Givens, B., and Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. *Brain Research Reviews*, **35**, 146–160.

Savazzi, S. (2003). Object-based versus object-centred neglect in reading words. *Neurocase*, **9**, 203–212.

Schall, J. D., and Boucher, L. (2007). Executive control of gaze by the frontal lobes. *Cognitive, Affective and Behavioral Neuroscience*, **7**, 396–412.

Schiff, N. D. (2008). Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Annals of the New York Academy of Sciences*, **1129**, 105–118.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, **448**, 600–603.

Schiller, P. H., Sandell, J. H., and Maunsell, J. H. R. (1987). The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. *Journal of Neurophysiology*, **57**, 1033–1049.

Schweizer, T. A., Kan, K., Hung, Y., Tam, F., Naglie, G., and Graham, S. J. (2013). Brain activity during driving with distraction: An immersive fMRI study. *Frontiers in*

Human Neuroscience, **7**, 53. <http://doi.org/10.3389/fnhum.2013.00053>

Serences, J., Schwarzbach, J., Courtney, S., Golay, X., and Yantis, S. (2004). Control of object-based attention in human cortex. *Cerebral Cortex*, **14**, 1346–1357.

Serino, A., Barbiani, M., Rinaldesi, M. L., and Ládavas, E. (2009). Effectiveness of prism adaptation in neglect rehabilitation: A controlled trial study. *Stroke*, **40**, 1392–1398.

Shindo, K., Sugiyama, K., Huabao, L., Nishijima, K., Kondo, T., and Izumi, S.-I. (2006). Long-term effect of low-frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. *Journal of Rehabilitation Medicine*, **38**, 65–67.

Shipp, S. (2003). The functional logic of cortico-pulvinar connections. *Philosophical Transactions of the Royal Society of London, Series B*, **358**, 1605–1624.

Shirani, P., Thorn, J., Davis, C., Heidler-Gary, J., Newhart, M., Gottesman, R. F., and Hillis, A. E. (2009). Severity of hypoperfusion in distinct brain regions predicts severity of hemispatial neglect in different reference frames. *Stroke*, **40**, 3563–3566.

Shomstein, S., and Yantis, S. (2006). Parietal cortex mediates voluntary control of spatial and nonspatial auditory attention. *Journal of Neuroscience*, **26**, 435–439.

Smallwood, J., and Andrews-Hanna, J. (2013). Not all minds that wander are lost: The importance of a balanced perspective on the mind-wandering state. *Frontiers in Psychology*, **4**, 441.

Smith, A. S., Boutrous, N. N., and Schwarzkopf, S. B. (1994). Reliability of P50 auditory event-related potential indices of sensory gating. *Psychophysiology*, **31**, 495–502.

Snow, J. C., Allen, H. A., Rafal, R. D., and Humphreys, G. W. (2009). Impaired

attentional selection following lesions to the human pulvinar: Evidence for homology between human and monkey. *Proceedings of the National Academy of Sciences*, **106**, 4054–4059.

Strayer, D. L., Drews, F. A., and Crouch, D. J. (2006). A comparison of the cellphone driver and the drunk driver. *Human Factors*, **48**, 381–391.

Strayer, D. L., Turrill, J., Cooper, J. M., Coleman, J. R., Medeiros-Ward, N., and Biondi, F. (2015). Assessing cognitive distraction in the automobile. *Human Factors*, **57**(8), 1300–1324. <http://doi.org/10.1177/0018720815575149>

Strumpf, H., Mangun, G. R., Boehler, C. N., Stoppel, C., Schoenfeld, M. A., Heinze, H.-J., and Hopf, J.-M. (2013). The role of the pulvinar in distractor processing and visual search. *Human Brain Mapping*, **34**(5), 1115–1132. <http://doi.org/10.1002/hbm.21496>

Sturm, W., de Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., et al. (1999). Functional anatomy of intrinsic alertness: Evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia*, **37**, 797–805.

Sturm, W., Longoni, F., Fimm, B., Dietrich, T., Weis, S., Kemna, S., et al. (2004). Network for auditory intrinsic alertness: A PET study. *Neuropsychologia*, **42**, 563–568.

Szameitat, A. J., Vanloo, A., and Müller, H. J. (2016). Central as well as peripheral attentional bottlenecks in dual-task performance activate lateral prefrontal cortices. *Frontiers in Human Neuroscience*, **10**, 119. <http://doi.org/10.3389/fnhum.2016.00119>

Taylor, P. C., Nobre, A. C., and Rushworth, M. F. (2007). Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: A combined transcranial magnetic stimulation electroencephalography study. *Journal of Neuroscience*, **27**, 11343–11353.

Ten Brink, A. F., Verwer, J. H., Biesbroek, J. M., Visser-Meily, J. M. A., and Nijboer, T. C. W. (2017). Differences between left- and right-sided neglect revisited: A large

cohort study across multiple domains. *Journal of Clinical and Experimental Neuropsychology*, **39**(7), 707–723.

Thimm, M., Fink, G. R., Küst, J., Karbe, H., Willmes, K., and Sturm, W. (2009). Recovery from hemineglect: Differential neurobiological effects of optokinetic stimulation and alertness training. *Cortex*, **45**, 850–862.

Treisman, A., and Gelade, G. (1980). A feature integration theory of attention. *Cognitive Psychology*, **12**, 97–136.

Treisman, A. M., and Schmidt, H. (1982). Illusory conjunctions in the perception of objects. *Cognitive Psychology*, **14**, 107–141.

Utz, K. S., Keller, I., Kardinal, M., and Kerkhoff, G. (2011). Galvanic vestibular stimulation reduces the pathological rightward line bisection error in neglect: A sham-stimulation-controlled study. *Neuropsychologia*, **49**, 1219–1225.

Vallar, G., and Bolognini, N. (2014). Unilateral spatial neglect. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 972–1027). Oxford: Oxford University Press.

Vallar, G., Guariglia, C., Nico, D., and Pizzamiglio, L. (1997). Motor deficits and optokinetic stimulation in patients with left hemineglect. *Neurology*, **49**, 1364–1370.

Vallar, G., Guariglia, C., and Rusconi, M. L. (1997). Modulation of neglect syndrome by sensory stimulation. In P. Theier and H. O. Karnath (eds.), *Parietal lobe contributions to orientation in 3D-space* (pp. 401–429). Heidelberg: Springer-Verlag.

Vallar, G., and Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical CT/slice study in man. *Neuropsychologia*, **24**, 609–622.

Vandenberghe, R., and Gillebert, C. R. (2009). Parcellation of parietal cortex:

Convergence between lesion-symptom mapping and mapping of the intact functioning brain. *Behavioural Brain Research*, **199**, 171–182.

van Voorhis, S., and Hillyard, S. A. (1977). Visual evoked potentials and selective attention to points in space. *Perception and Psychophysics*, **22**, 54–62.

Vohn, R., Fimm, B., Weber, J., Schnitker, R., Thron, A., Spijkers, W., et al. (2007). Management of attentional resources in within-modal and cross-modal divided attention tasks: An fMRI study. *Human Brain Mapping*, **28**, 1267–1275.

Vossel, S., Geng, J. J., and Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *The Neuroscientist*, **20**(2), 150–159.
<http://doi.org/10.1177/1073858413494269>

Vuilleumier, P., Sagiv, N., Hazeltine, E., Poldrack, R. A., Swick, D., Rafal, R. D., and Gabrieli, J. D. E. (2001). Neural fate of seen and unseen faces in visuospatial neglect: A combined event-related functional MRI and event-related potential study. *Proceedings of the National Academy of Sciences*, **98**, 3495–3500.

Wardak, C., Olivier, E., Duhamel, J. R. (2004). A deficit in covert attention after parietal cortex inactivation in the monkey. *Neuron*, **42**, 501–508.

Wardak, C., Ibos, G., Duhamel, J. R., and Olivier, E. (2006). Contribution of the monkey frontal eye field to covert visual attention. *Journal of Neuroscience*, **26**, 4228–4235.

Watson, J. M., and Strayer, D. L. (2010). Supertaskers: Profiles in extraordinary multitasking ability. *Psychonomic Bulletin and Review*, **17**(4), 479–485.

Webb, T. W., Igelström, K. M., Schurger, A., and Graziano, M. S. A. (2016). Cortical networks involved in visual awareness independent of visual attention. *Proceedings of the National Academy of Sciences*, **113**(48), 13923–13928.
<http://doi.org/10.1073/pnas.1611505113>

Weintraub, S., and Mesulam, M. (1987). Right cerebral dominance in spatial attention. *Archives of Neurology*, **44**, 621–625.

Weissman, D. H., Roberts, K. C., Visscher, K. M., and Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, **9**, 971–978.

Wickens, C., Kramer, A., Vanasse, L., and Donchin, E. (1983). Performance of concurrent tasks: A psychophysiological analysis of the reciprocity of information-processing resources. *Science*, **221**, 1080–1082.

Wickens, C. D. (1980). The structure of attentional resources. In R. Nickerson and R. Pew (eds.), *Attention and performance*, VIII. Hillsdale, NJ: Erlbaum.

Wojciulik, E., and Kanwisher, N. (1999). The generality of parietal involvement in visual attention. *Neuron*, **23**, 747–764.

Wolfe, J. M. (2014). Approaches to visual search. In A. C. K. Nobre and S. Kastner (eds.), *The Oxford handbook of attention* (pp. 11–55). Oxford: Oxford University Press.

Wurtz, R. H., and Goldberg, M. E. (1972). Activity of superior colliculus in behaving monkey: III. Cells discharging before eye movements. *Journal of Neurophysiology*, **35**, 575–586.

Wyart, V., and Tallon-Baudry, C. (2008). Neural dissociation between visual awareness and spatial attention. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **28**(10), 2667–2679.

<http://doi.org/10.1523/JNEUROSCI.4748-07.2008>

Xuan, B., Mackie, M.-A., Spagna, A., Wu, T., Tian, Y., Hof, P. R., and Fan, J. (2016). The activation of interactive attentional networks. *NeuroImage*, **129**, 308–319.

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J., and Courtney, S. M. (2002). Transient neural activity in human parietal cortex

during spatial attention shifts. *Nature Neuroscience*, **5**, 995–1002.

Yantis, S., and Serences, J. T. (2003). Cortical mechanisms of space-based and object-based attentional control. *Current Opinion in Neurobiology*, **13**, 187–193.

Yokoyama, K., Jennings, R., Ackles, P., Hood, P., and Boller, F. (1987). Lack of heart rate changes during an attention-demanding task after right hemisphere lesions. *Neurology*, **37**, 624–630.

Young, A. W., DeHaan, E. H. F., Newcombe, F., and Hay, D. C. (1990). Facial neglect. *Neuropsychologia*, **28**, 391–415.

Young, A. W., Hellawell, D. J., and Welch, J. (1992). Neglect and visual recognition. *Brain*, **115**, 51–71.

Young, G. B. (2009). Coma. *Annals of the New York Academy of Sciences*, **1157**, 32–47.

Yue, Y., Song, W., Huo, S., and Wang, M. (2012). Study on the occurrence and neural bases of hemispatial neglect with different reference frames. *Archives of Physical Medicine and Rehabilitation*, **93**, 156–162.

Zhang, W., and Luck, S. J. (2009). Feature-based attention modulates feedforward visual processing. *Nature Neuroscience*, **12**, 24–25.

Chapter 11

Aichelburg, C., Urbanski, M., Thiebaut de Schotten, M., Humbert, F., Levy, R., and Volle, E. (2016). Morphometry of left frontal and temporal poles predicts analogical reasoning abilities. *Cerebral Cortex*, **26**(3), 915–932.

<http://doi.org/10.1093/cercor/bhu254>

Alexander, W. H., and Brown, J. W. (2011). Medial prefrontal cortex as an action-outcome predictor. *Nature Neuroscience*, **14**(10), 1338–1344.

<http://doi.org/10.1038/nn.2921>

Amiez, C., and Petrides, M. (2007). Selective involvement of the mid-dorsolateral prefrontal cortex in the coding of the serial order of visual stimuli in working memory. *Proceedings of the National Academy of Sciences*, **104**, 13786–13791.

Anderson, M. C., and Green, C. (2001). Suppressing unwanted memories by executive control. *Nature*, **410**(6826), 366–369.

Anderson, M. C., Ochsner, K. N., Kuhl, B., Cooper, J., Robertson, E., Gabrieli, S. W., et al. (2004). Neural systems underlying the suppression of unwanted memories. *Science*, **303**(5655), 232–235.

Andrews-Hanna, J. R., Mackiewicz Seghete, K. L., Claus, E. D., Burgess, G. C., Ruzic, L., and Banich, M. T. (2011). Cognitive control in adolescence: Neural underpinnings and relation to self-report behaviors. *PLoS ONE*, **6**(6), e21598.

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., and Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, **6**, 115–116.

Aron, A. R., Monsell, S., Sahakian, B. J., and Robbins, T. W. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain*, **127**, 1561–1573.

Aron, A. R., Robbins, T. W., and Poldrack, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, **8**(4), 170–177.

Aron, A. R., Robbins, T. W., and Poldrack, R. A. (2014). Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*, **18**(4), 177–185.

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences*, **12**, 193–200.

Badre, D., and D'Esposito, M. (2009). Is the rostro-caudal axis of the frontal lobe hierarchical? *Nature Reviews Neuroscience*, **10**, 659–669.

Bahlmann, J., Beckmann, I., Kuhlehn, I., Schweikard, A., and Münte, T. F. (2015). Transcranial magnetic stimulation reveals complex cognitive control representations in the rostral frontal cortex. *Neuroscience*, **300**, 425–431.

Banich, M. T. (2009). Executive function: The search for an integrated account. *Current Directions in Psychological Science*, **18**, 89–94.

Banich, M. T., Mackiewicz Seghete, K. L., Depue, B. E., and Burgess, G. C. (2015). Multiple modes of clearing one's mind of current thoughts: Overlapping and distinct neural systems. *Neuropsychologia*, **69**, 105–117.

Banich, M. T., Milham, M. P., Atchley, R. A., Cohen, N. J., Webb, A., Wszalek, T., et al. (2000). Prefrontal regions play a predominant role in imposing an attentional “set”: Evidence from fMRI. *Cognitive Brain Research*, **10**(1–2), 1–9.

[http://doi.org/10.1016/S0926-6410\(00\)00015-X](http://doi.org/10.1016/S0926-6410(00)00015-X)

Baxter, M. G. (2009). Prefrontal cortex and rule abstraction: Where and whether? Theoretical comment on Moore et al. (2009). *Behavioral Neuroscience*, **123**, 459–462.

Bengtsson, S. L., Haynes, J. D., Sakai, K., Buckley, M. J., and Passingham, R. E.

(2009). The representation of abstract task rules in the human prefrontal cortex. *Cerebral Cortex*, **19**, 1929–1936.

Bonnelle, V., Manohar, S., Behrens, T., and Husain, M. (2016). Individual differences in premotor brain systems underlie behavioral apathy. *Cerebral Cortex*, **26**(2), 807–819.

Boorman, E. D., Behrens, T. E., Woolrich, M. W., and Rushworth, M. F. (2009). How green is the grass on the other side? Frontopolar cortex and the evidence in favor of alternative courses of action. *Neuron*, **62**, 733–743.

Boschin, E. A., Piekema, C., and Buckley, M. J. (2015). Essential functions of primate frontopolar cortex in cognition. *Proceedings of the National Academy of Sciences*, **112**(9), E1020–1027.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., and Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, **108**, 624–652.

Botvinick, M., Cohen, J. D., and Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, **8**, 539–546.

Braver, T. S., and Barch, D. M. (2006). Extracting core components of cognitive control. *Trends in Cognitive Science*, **10**(12), 529–532.

<http://doi.org/10.1016/j.tics.2006.10.006>

Braver, T. S., and Bongiolatti, S. R. (2002). The role of frontopolar cortex in subgoal processing during working memory. *NeuroImage*, **15**, 523–536.

Bunge, S. A. (2004). How we use rules to select actions: A review of evidence from cognitive neuroscience. *Cognitive, Affective, and Behavioral Neuroscience*, **4**(4), 564–579.

Cai, W., Ryali, S., Chen, T., Li, C.-S. R., and Menon, V. (2014). Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: Evidence from

intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. *The Journal of Neuroscience*, **34**(44), 14652–14667. <http://doi.org/10.1523/JNEUROSCI.3048-14.2014>

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., and Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, **280**, 747–749.

Chatham, C. H., Claus, E. D., Kim, A., Curran, T., Banich, M. T., and Munakata, Y. (2012). Cognitive control reflects context monitoring, not motoric stopping, in response inhibition. *PLoS ONE*, **7**(2), e31546.

Chevalier, N., Chatham, C. H., and Munakata, Y. (2014). Practice of going helps children to stop: The importance of context monitoring in inhibitory control. *Journal of Experimental Psychology: General*, **143**(3), 959–965.

Chi, R. P., and Snyder, A. W. (2011). Facilitate insight by non-invasive brain stimulation. *PLoS ONE*, **6**(2), e16655

Chi, R. P., and Snyder, A. W. (2012). Brain stimulation enables the solution of an inherently difficult problem. *Neuroscience Letters*, **515**, 121–124.

Chrysikou, E. G., Hamilton, R. H., Coslett, H. B., Datta, A., Bikson, M., and Thompson-Schill, S. L. (2013). Noninvasive transcranial direct current stimulation over the left prefrontal cortex facilitates cognitive flexibility in tool use. *Cognitive Neuroscience*, **4**(2), 81–89.

Cicerone, K., Lazar, R., and Shapiro, W. (1983). Effects of frontal lobe lesions on hypothesis sampling during concept formation. *Neuropsychologia*, **21**, 513–524.

Cools, R. (2016). The costs and benefits of brain dopamine for cognitive control. *Wiley Interdisciplinary Reviews: Cognitive Science*, **7**(5), 317–329.

Courchesne, E., Hillyard, S. A., and Galambos, R. (1975). Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephology and Clinical Neurophysiology*, **39**, 131–143.

Coutlee, C. G., and Huettel, S. A. (2012). The functional neuroanatomy of decision making: Prefrontal control of thought and action. *Brain Research*, **1428**, 3–12.

Craig, A. D. B. (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Annals of the New York Academy of Sciences*, **1225**(1), 72–82.

Criaud, M., and Boulinguez, P. (2013). Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. *Neuroscience and Biobehavioral Reviews*, **37**(1), 11–23.

Cristofori, I., Zhong, W., Chau, A., Solomon, J., Krueger, F., and Grafman, J. (2015). White and gray matter contributions to executive function recovery after traumatic brain injury. *Neurology*, **84**(14), 1394–1401.

Cromer, J. A., Roy, J. E., and Miller, E. K. (2010). Representation of multiple, independent categories in the primate prefrontal cortex. *Neuron*, **66**(5), 796–807.

Davies, P. L., Segalowitz, S. J., Dywan, J., and Pailing, P. E. (2001). Error-negativity and positivity as they relate to other ERP indices of attentional control and stimulus processing. *Biological Psychology*, **56**(3), 191–206.

Daw, N. D., O'Doherty, J. P., Dayan, P., Seymour, B., and Dolan, R. J. (2006). Cortical substrates for exploratory decisions in humans. *Nature*, **441**(7095), 876–879.

Debelak, R., Egle, J., Köstering, L., and Kaller, C. P. (2016). Assessment of planning ability: Psychometric analyses on the unidimensionality and construct validity of the Tower of London Task (TOL-F). *Neuropsychology*, **30**(3), 346–360.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D. Y., and Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience*, **25**, 11730–11737.

Dehaene, S., Posner, M. I., and Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science*, **5**, 303–305.

Delis, D. C., Squire, L. R., Bihle, A., and Massman, P. (1992). Componential analysis of problem-solving ability: Performance of patients with frontal lobe damage and amnesic patients on a new sorting test. *Neuropsychologia*, **30**, 683–697.

Della Malva, C. L., Stuss, D. T., D'Alton, J., and Willmer, J. (1993). Capture errors and sequencing after frontal brain lesions. *Neuropsychologia*, **31**, 363–372.

Demakis, G. J. (2003). A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage. *Neuropsychology*, **17**, 255–264.

Demanet, J., de Baene, W., Arrington, C. M., and Brass, M. (2013). Biasing free choices: The role of the rostral cingulate zone in intentional control. *NeuroImage*, **72**, 207–213.

Depue, B. E. (2012). A neuroanatomical model of prefrontal inhibitory modulation of memory retrieval. *Neuroscience and Biobehavioral Reviews*, **36**(5), 1382–1399.

Depue, B. E., Burgess, G. C., Willcutt, E. G., Ruzic, L., and Banich, M. T. (2010). Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: Evidence from deficits in individuals with ADHD. *Neuropsychologia*, **48**(13), 3909–3917.

Depue, B. E., Curran, T., and Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*, **317**(5835),

215–219.

Depue, B. E., Orr, J. M., Smolker, H. R., Naaz, F., and Banich, M. T. (2015). The organization of right prefrontal networks reveals common mechanisms of inhibitory regulation across cognitive, emotional, and motor processes. *Cerebral Cortex*, **26**(4), 1634–1646.

Derrfuss, J., Brass, M., Neumann, J., and von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and Stroop studies. *Human Brain Mapping*, **25**, 22–34.

Desrochers, T. M., Chatham, C. H., and Badre, D. (2015). The necessity of rostrolateral prefrontal cortex for higher-level sequential behavior. *Neuron*, **87**(6), 1357–1368.
<http://doi.org/10.1016/j.neuron.2015.08.026>

Dhar, M., Wiersema, J. R., and Pourtois, G. (2011). Cascade of neural events leading from error commission to subsequent awareness revealed using EEG source imaging. *PLoS ONE*, **6**(5), e19578.

Dockery, C. A., Hueckel-Weng, R., Birbaumer, N., and Plewnia, C. (2009). Enhancement of planning ability by transcranial direct current stimulation. *Journal of Neuroscience*, **29**, 7271–7277.

Dosenbach, N. U. F., Visscher, K. M., Palmer, E. D., Miezin, F. M., Wenger, K. K., Kang, H. C., et al. (2006). A core system for the implementation of task sets. *Neuron*, **50**(5), 799–812.

Dreher, J. C., Koechlin, E., Tierney, M., and Grafman, J. (2008). Damage to the fronto-polar cortex is associated with impaired multitasking. *PLoS ONE*, **3**, e3227.

Duncan, J. (1986). Disorganization of behavior after frontal lobe damage. *Cognitive Neuropsychology*, **3**, 271–290.

Duncan, J. (2013). The structure of cognition: Attentional episodes in mind and brain. *Neuron*, **80**(1), 35–50.

Duncan, J., and Owen, A. M. (2000). Cognitive regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences*, **23**, 475–483.

Evans, L. H., Herron, J. E., and Wilding, E. L. (2015). Direct real-time neural evidence for task-set inertia. *Psychological Science*, **26**(3), 284–290.

Falkenstein, M., Hohnsbein, J., Hoormann, J., and Blanke, L. (1991). Effects of cross-modal divided attention on late ERP components: II. Error processing in choice reaction tasks. *Clinical Neurophysiology*, **78**(6), 447–455.

Fedorenko, E., Duncan, J., and Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, **110**(41), 16616–16621.

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. *Nature Neuroscience*, **13**, 538–539.

Fitzgerald, K. D., Welsh, R. C., Gehring, W. J., Abelson, J. L., Himle, J. A., Liberzon, I., and Taylor, S. F. (2005). Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biological Psychiatry*, **57**(3), 287–294.

Ford, J. M., Sullivan, E. V., Marsh, L., White, P. M., Lim, K. O., and Pfefferbaum, A. (1994). The relationship between P300 amplitude and regional gray matter volumes depends upon the attentional system engaged. *Electroencephalography and Clinical Neurophysiology*, **90**, 214–228.

Forstmann, B. U., Brass, M., Koch, I., and von Cramon, D. Y. (2006). Voluntary selection of task sets revealed by functional magnetic resonance imaging. *Journal of*

Cognitive Neuroscience, **18**, 388–398.

Franken, I. H., van Strien, J. W., Franzek, E. J., and van de Wetering, B. J. (2007). Error-processing deficits in patients with cocaine dependence. *Biological Psychology*, **75**, 45–51.

Freedman, D. J., Riesenhuber, M., Poggio, T., and Miller, E. K. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. *Science*, **291**(5502), 312–316.

Friedman, D., Goldman, R., Stern, Y., and Brown, T. R. (2009). The brain's orienting response: An event-related functional magnetic resonance imaging investigation. *Human Brain Mapping*, **30**, 1144–1154.

Fuster, J. M. (1985). The prefrontal cortex, mediator of cross-temporal contingencies. *Human Neurobiology*, **4**, 169–179.

Fuster, J. M. (1989). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe*. New York: Raven Press.

Garrigan, B., Adlam, A. L. R., and Langdon, P. E. (2016). The neural correlates of moral decision-making: A systematic review and meta-analysis of moral evaluations and response decision judgements. *Brain and Cognition*, **108**, 88–97.

Gehring, W. J., and Knight, R. T. (2000). Prefrontal-cingulate interactions in action monitoring. *Nature Neuroscience*, **3**, 516–520.

Gehring, W. J., Liu, Y., Orr, J. M., and Carp, J. (2012). The error-related negativity (ERN/Ne). In E. S. Kappenman and S. J. Luck (eds.), *The Oxford handbook of event-related potentials* (pp. 231–291). New York: Oxford University Press.

Gehring, W. J., and Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science*, **295**, 2279–2282.

Gehring, W. P., Goss, B., Coles, M. G. H., Meyer, D. E., and Donehin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, **4**(6), 385–390.

Gelfand, J. R., and Bookheimer, S. Y. (2003). Dissociating neural mechanisms of temporal sequencing and processing phonemes. *Neuron*, **38**(5), 831–842.

Genovesio, A., Brasted, P. J., and Wise, S. P. (2006). Representation of future and previous spatial goals by separate neural populations in prefrontal cortex. *The Journal of Neuroscience*, **26**(27), 7305–7316.

Ghahremani, D. G., Monterosso, J., Jentsch, J. D., Bilder, R. M., and Poldrack, R. A. (2009). Neural components underlying behavioral flexibility in human reversal learning. *Cerebral Cortex*, e-publication in advance of print.

Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., et al. (2012). Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proceedings of the National Academy of Sciences*, **109**(36), 14681–14686.

Goschke, T. (2013). Volition in action: Intentions, control dilemmas and the dynamic regulation of cognitive intentional control. In W. Prinz, A. Beisert, and A. Herwig (eds.), *Action science: Foundations of an emerging discipline* (pp. 409–434). Cambridge, MA: MIT Press.

Gratton, G., Wee, E., Rykhlevskaia, E. I., Leaver, E. E., and Fabiani, M. (2009). Does white matter matter? Spatio-temporal dynamics of task switching in aging. *Journal of Cognitive Neuroscience*, **21**, 1380–1395.

Green, A. E., Fugelsang, J. A., Kraemer, D. J., Shamosh, N. A., and Dunbar, K. N. (2006). Frontopolar cortex mediates abstract integration in analogy. *Brain Research*, **1096**, 125–137.

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., and Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *NeuroImage*, **50**(3), 1313–1319.

Hare, T., Camerer, C., and Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*, **324**, 646.

Haynes, J. D., Sakai, K., Rees, G., Gilbert, S., Frith, C., and Passingham, R. E. (2007). Reading hidden intentions in the human brain. *Current Biology*, **17**, 323–328.

Hazy, T. E., Frank, M. J., and O'Reilly, R. C. (2006). Banishing the homunculus: Making working memory work. *Neuroscience*, **139**, 105–118.

Heinze, K., Ruh, N., Nitschke, K., Reis, J., Fritsch, B., Unterrainer, J. M., et al. (2014). Transcranial direct current stimulation over left and right DLPFC: Lateralized effects on planning performance and related eye movements. *Biological Psychology*, **102**, 130–140.

Hester, R., Foxe, J. J., Molholm, S., Shpaner, M., and Garavan, H. (2005). Neural mechanisms involved in error processing: A comparison of errors made with and without awareness. *NeuroImage*, **27**(3), 602–608.

Hobeika, L., Diard-Detoeuf, C., Garcin, B., Levy, R., and Volle, E. (2016). General and specialized brain correlates for analogical reasoning: A meta-analysis of functional imaging studies. *Human Brain Mapping*, **37**(5), 1953–1969.

Hochman, E. Y., Wang, S., Milner, T. E., and Fellows, L. K. (2015). Double dissociation of error inhibition and correction deficits after basal ganglia or dorsomedial frontal damage in humans. *Neuropsychologia*, **69**, 130–139.

Hoerold, D., Pender, N. P., and Robertson, I. H. (2013). Metacognitive and online error awareness deficits after prefrontal cortex lesions. *Neuropsychologia*, **51**(3), 385–391.

Holroyd, C. B., and Coles, M. G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, **109**, 679–709.

Holroyd, C. B., and Coles, M. G. (2008). Dorsal anterior cingulate cortex integrates reinforcement history to guide voluntary behavior. *Cortex*, **44**, 548–559.

Holroyd, C. B., Nieuwenhuis, S., Yeung, N., and Cohen, J. D. (2003). Errors in reward prediction are reflected in the event-related brain potential. *NeuroReport*, **14**(18), 2481–2484.

Hoonakker, M., Doignon-Camus, N., and Bonnefond, A. (2016). Performance monitoring mechanisms activated before and after a response: A comparison of aware and unaware errors. *Biological Psychology*, **120**, 53–60, figure 3b, page 57.

Hosokawa, T., Kennerley, S. W., Sloan, J., and Wallis, J. D. (2013). Single-neuron mechanisms underlying cost-benefit analysis in frontal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **33**(44), 17385–17397.

Hulbert, J. C., Henson, R. N., and Anderson, M. C. (2016). Inducing amnesia through systemic suppression. *Nature Communications*, **7**, 11003.

Hyafil, A., Summerfield, C., and Koechlin, E. (2009). Two mechanisms for task switching in the prefrontal cortex. *Journal of Neuroscience*, **29**, 5135–5142.

Jahn, A., Nee, D. E., Alexander, W. H., and Brown, J. W. (2014). Distinct regions of anterior cingulate cortex signal prediction and outcome evaluation. *NeuroImage*, **95**, 80–89.

Jung-Beeman, M., Bowden, E. M., Haberman, J., Frymiare, J. L., Arambel-Liu, S., et al. (2004). Neural activity when people solve verbal problems with insight. *PLoS Biology*,

2(4), e97.

Kable, J. W., and Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, **10**(12), 1625–1633.

Kaller, C. P., Rahm, B., Spreer, J., Weiller, C., and Unterrainer, J. M. (2011). Dissociable contributions of left and right dorsolateral prefrontal cortex in planning. *Cerebral Cortex*, **21**(2), 307–317.

Kaller, C. P., Reiser, M., Katzev, M., Umarova, R., Mader, I., Hennig, J., et al. (2015). Predicting planning performance from structural connectivity between left and right mid-dorsolateral prefrontal cortex: Moderating effects of age during postadolescence and midadulthood. *Cerebral Cortex*, **25**(4), 869–883.

Karitonova, M., Chien, S., Colunga, E., and Munakata, Y. (2009). More than a matter of getting “unstuck”: Flexible thinkers use more abstract representations than perseverators. *Developmental Science*, **12**, figure 2, page 665.

Kehagia, A. A., Barker, R. A., and Robbins, T. W. (2014). Revisiting the effects of Parkinson’s disease and frontal lobe lesions on task switching: The role of rule reconfiguration. *Journal of Neuropsychology*, **8**(1), 53–74.

Keil, J., Weisz, N., Paul-Jordanov, I., and Wienbruch, C. (2010). Localization of the magnetic equivalent of the ERN and induced oscillatory brain activity. *NeuroImage*, **51**(1), 404–411.

Kharitonova, M., Chien, S., Colunga, E., and Munakata, Y. (2009). More than a matter of getting “unstuck”: Flexible thinkers use more abstract representations than perseverators. *Developmental Science*, **12**(4), 662–669.

Kieffaber, P. D., Hershaw, J., Sredl, J., and West, R. (2016). Electrophysiological correlates of error initiation and response correction. *NeuroImage*, **128**, 158–166.

Kiehl, K. A., Liddle, P. F., and Hopfinger, J. B. (2000). Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology*, **37**, 216–223.

Kiehl, K. A., Laurens, K. R., Duty, T. L., Forster, B. B., and Liddle, P. F. (2001). Neural sources involved in auditory target detection and novelty processing: An event-related fMRI study. *Psychophysiology*, **38**(1), 133–142.

Kim, C., Cilles, S. E., Johnson, N. F., and Gold, B. T. (2012). Domain general and domain preferential brain regions associated with different types of task switching: A meta-analysis. *Human Brain Mapping*, **33**(1), 130–142.

Kim, C., Kroger, J. K., Calhoun, V. D., and Clark, V. P. (2015). The role of the frontopolar cortex in manipulation of integrated information in working memory. *Neuroscience Letters*, **595**, 25–29.

Klein-Flügge, M. C., Kennerley, S. W., Friston, K., and Bestmann, S. (2016). Neural signatures of value comparison in human cingulate cortex during decisions requiring an effort-reward trade-off. *The Journal of Neuroscience*, **36**(39), 10002–10015.

Kleinman, J. T., DuBois, J. C., Newhart, M., and Hillis, A. E. (2013). Disentangling the neuroanatomical correlates of perseveration from unilateral spatial neglect. *Behavioural Neurology*, **26**(1–2), 131–138.

Knoblich, G., Ohlsson, S., Haider, H., and Rhenius, D. (1999). Constraint relaxation and chunk decomposition in insight problem solving. *Journal of Experimental Psychology: Learning, Memory and Cognition*, **25**, 1534–1555.

Knutson, K. M., Dal Monte, O., Schintu, S., Wassermann, E. M., Raymont, V., Grafman, J., and Krueger, F. (2015). Areas of brain damage underlying increased reports of behavioral disinhibition. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **27**(3), 193–198.

Koechlin, E., and Summerfield, C. (2007). An information theoretical approach to prefrontal executive function. *Trends in Cognitive Sciences*, **11**, 229–235.

Konishi, S., Morimoto, H., Jimura, K., Asari, T., Chikazoe, J., Yamashita, K., et al. (2008). Differential superior prefrontal activity on initial versus subsequent shifts in naive subjects. *NeuroImage*, **41**, 575–580.

Kounios, J., and Beeman, M. (2014). The cognitive neuroscience of insight. *Annual Review of Psychology*, **65**, 71–93.

Krämer, U. M., Solbakk, A.-K., Funderud, I., Løvstad, M., Endestad, T., and Knight, R. T. (2013). The role of the lateral prefrontal cortex in inhibitory motor control. *Cortex*, **49**(3), 837–849.

Leite, J., Carvalho, S., Fregni, F., Boggio, P. S., and Gonçalves, O. F. (2013). The effects of cross-hemispheric dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS) on task switching. *Brain Stimulation*, **6**(4), 660–667.

Lezak, M. D., Howieson, D. B., Bigler, E. D., and Tranel, D. (2012). *Neuropsychological assessment* (5th edn.). Oxford: Oxford University Press.

Lhermitte, F. (1983). “Utilization behavior” and its relation to lesions of the frontal lobes. *Brain*, **106**, 237–255.

Lhermitte, F. (1986). Human autonomy and the frontal lobes: Part II. Patient behavior in complex and social situations: The “Environmental Dependency Syndrome.” *Annals of Neurology*, **19**(4), 335–343.

Lhermitte, F., Pillon, B., and Serdaru, M. (1986). Human autonomy and the frontal lobes: Part I. Imitation and utilization behavior: A neuropsychological study of 75 patients. *Annals of Neurology*, **19**, 326–334.

Li, C. S., Huang, C., Constable, R. T., and Sinha, R. (2006). Imaging response inhibition

in a stop-signal task: Neural correlates independent of signal monitoring and post-response processing. *Journal of Neuroscience*, **26**, 186–192.

Luria, A. R. (1966). *Higher cortical functions in man*. New York: Basic Books.

Luu, P., Collins, P., and Tucker, D. M. (2000). Mood, personality, and self-monitoring: Negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology General*, **129**, 43–60.

MacDonald, A. W., Cohen, J. D., Stenger, V. W., and Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, **288**, 1835–1838.

Mansouri, F. A., Buckley, M. J., Mahboubi, M., and Tanaka, K. (2015). Behavioral consequences of selective damage to frontal pole and posterior cingulate cortices. *Proceedings of the National Academy of Sciences*, **112**(29), E3940–9.

Mansouri, F. A., Rosa, M. G. P., and Atapour, N. (2015). Working memory in the service of executive control functions. *Frontiers in Systems Neuroscience*, **9**, 166.

Massimo, L., Powers, J. P., Evans, L. K., McMillan, C. T., Rascovsky, K., Eslinger, P., et al. (2015). Apathy in frontotemporal degeneration: Neuroanatomical evidence of impaired goal-directed behavior. *Frontiers in Human Neuroscience*, **9**, 611.

McClure, S., Laibson, D., Loewenstein, G., and Cohen, J. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, **306**, 503.

Metuki, N., Sela, T., and Lavidor, M. (2012). Enhancing cognitive control components of insight problem solving by anodal tDCS of the left dorsolateral prefrontal cortex. *Brain Stimulation*, **5**, 110–115.

Milham, M. P., Erickson, K. I., Banich, M. T., Kramer, A. F., Webb, A., Wszalek, T., and Cohen, N. J. (2002). Attentional control in the aging brain: Insights from an fMRI study

of the Stroop task. *Brain and Cognition*, **49**, 277–296.

Miller, E. K., and Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, **24**, 167–202.

Milner, B. (1963). Effects of different brain lesions on card sorting: The role of the frontal lobes. *Archives of Neurology*, **9**, 100–110.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin*, **27**, 272–277.

Milner, B. (1982). Some cognitive effects of frontal-lobe lesions in man. *Philosophical Transactions of the Royal Society of London, Series B*, **298**, 211–226.

Milner, B., Corsi, P., and Leonard, G. (1991). Frontal-lobe contribution to recency judgements. *Neuropsychologia*, **29**, 601–618.

Miyake, A., and Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science: A Journal of the American Psychological Society*, **21**(1), 8–14. <http://doi.org/10.1177/0963721411429458>

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. *Cognitive Psychology*, **41**, 49–100.

Mok, V. C. T., Liu, T., Lam, W. W. M., Wong, A., Hu, X., Guo, L., et al. (2008). Neuroimaging predictors of cognitive impairment in confluent white matter lesion: Volumetric analyses of 99 brain regions. *Dementia and Geriatric Cognitive Disorders*, **25**(1), 67–73. <http://doi.org/10.1159/000111692>

Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences*, **7**, 134–140.

Moser, J. S., Moran, T. P., Schroder, H. S., Donnellan, M. B., and Yeung, N. (2013). On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework. *Frontiers in Human Neuroscience*, **7**, 466.

Munakata, Y., Herd, S. A., Chatham, C. H., Depue, B. E., Banich, M. T., and O'Reilly, R. C. (2011). A unified framework for inhibitory control. *Trends in Cognitive Sciences*, **15**(10), 453–459.

Munakata, Y., Snyder, H. R., and Chatham, C. H. (2012). Developing cognitive control: Three key transitions. *Current Directions in Psychological Science*, **21**(2), 71–77.

Mutha, P. K., Stapp, L. H., Sainburg, R. L., and Haaland, K. Y. (2014). Frontal and parietal cortex contributions to action modification. *Cortex*, **57**, 38–50.

Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Oyanagi, C., et al. (2001). Dissociable mechanisms of attentional control within the human prefrontal cortex. *Cerebral Cortex*, **11**, 85–92.

Nee, D. E., and Jonides, J. (2014). Frontal-medial temporal interactions mediate transitions among representational states in short-term memory. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **34**(23), 7964–7975.

Nee, D. E., Wager, T. D., and Jonides, J. (2007). Interference resolution: Insights from a meta-analysis of neuroimaging tasks. *Cognitive, Affective, and Behavioral Neuroscience*, **7**, 1–17.

Neta, M., Nelson, S. M., and Petersen, S. E. (2016). Dorsal anterior cingulate, medial superior frontal cortex, and anterior insula show performance reporting-related late task control signals. *Cerebral Cortex*, e-publication in advance of print.

Newman, S. D., Carpenter, P. A., Varma, S., and Just, M. A. (2003). Frontal and parietal

participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*, **41**, 1668–1682.

Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H., and Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, **38**(5), 752–760.

Nitschke, K., Köstering, L., Finkel, L., Weiller, C., and Kaller, C. P. (2017). A Meta-analysis on the neural basis of planning: Activation likelihood estimation of functional brain imaging results in the Tower of London task. *Human Brain Mapping*, **38**(1), 396–413.

Nyhus, E., and Barceló, F. (2009). The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: A critical update. *Brain and Cognition*, **71**, 437–451.

O'Reilly, R. C., Herd, S. A., and Pauli, W. M. (2010). Computational models of cognitive control. *Current Opinion in Neurobiology*, **20**(2), 257–261.

Orr, J. M., and Banich, M. T. (2014). The neural mechanisms underlying internally and externally guided task selection. *NeuroImage*, **84**, 191–205.
<http://doi.org/10.1016/j.neuroimage.2013.08.047>

Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J., and Robbins, T. W. (1991). Extra-dimensional versus intradimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalohippocampectomy in man. *Neuropsychologia*, **29**, 993–1006.

Petrides, M. (2007). The orbitofrontal cortex: Novelty, deviation from expectation, and memory. *Annals of the New York Academy of Sciences*, **1121**, 33–53.

Petrides, M., and Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia*, **20**, 249–262.

Phillips, J. M., Vinck, M., Everling, S., and Womelsdorf, T. (2014). A long-range fronto-parietal 5- to 10-Hz network predicts “top-down” controlled guidance in a task-switch paradigm. *Cerebral Cortex*, **24**(8), 1996–2008.

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, **118**(10), 2128–2148, figure 5, page 2135.

Pourtois, G., Vocat, R., N'diaye, K., Spinelli, L., Seeck, M., and Vuilleumier, P. (2010). Errors recruit both cognitive and emotional monitoring systems: Simultaneous intracranial recordings in the dorsal anterior cingulate gyrus and amygdala combined with fMRI. *Neuropsychologia*, **48**(4), 1144–1159.

Prigatano, G. P., Altman, I. M., and O'Brien, K. P. (1990). Behavioral limitations that traumatic-brain-injured patients tend to underestimate. *Clinical Neuropsychologist*, **4**, 163–176.

Proudfit, G. H., Inzlicht, M., and Mennin, D. S. (2013). Anxiety and error monitoring: The importance of motivation and emotion. *Frontiers in Human Neuroscience*, **7**, 636.

Qiu, J., Li, H., Chen, A., and Zhang, Q. (2008). The neural basis of analogical reasoning: An event-related potential study. *Neuropsychologia*, **46**, 3006–3013.

Ragozzino, M. E. (2007). The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Annals of the New York Academy of Sciences*, **1121**, 355–375.

Ramnani, N., and Owen, A. M. (2004). Anterior prefrontal cortex: Insights into function from anatomy and neuroimaging. *Nature Reviews Neuroscience*, **5**, 184–194.

Ranti, C., Chatham, C. H., and Badre, D. (2015). Parallel temporal dynamics in hierarchical cognitive control. *Cognition*, **142**, 205–229.

Ravizza, S. M., and Carter, C. S. (2008). Shifting set about task switching: Behavioral and neural evidence for distinct forms of cognitive flexibility. *Neuropsychologia*, **46**, 2924–2935.

Reverberi, C., D'Agostini, S., Skrap, M., and Shallice, T. (2005). Generation and recognition of abstract rules in different frontal lobe subgroups. *Neuropsychologia*, **43**, 1924–1937.

Reverberi, C., Toraldo, A., D'Agostini, S., and Skrap, M. (2005). Better without (lateral) frontal cortex? Insight problems solved by frontal patients. *Brain*, **128**, 2882–2890.

Rieger, M., Gaugel, S., and Burmeister, K. (2003). Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. *Neuropsychology*, **17**(2), 272–282.

Roberts, R. E., and Husain, M. (2015). A dissociation between stopping and switching actions following a lesion of the pre-supplementary motor area. *Cortex*, **63**, 184–195.

Rogers, R. D., Andrews, T. C., Grasby, P. M., Brooks, D. J., and Robbins, T. W. (2000). Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. *Journal of Cognitive Neuroscience*, **12**, 142–162.

Rogers, R. D., Sahakian, B. J., Hodges, J. R., Polkey, C. E., Kennard, C., and Robbins, T. W. (1998). Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain*, **121**(Pt. 5), 815–842.

Rougier, N. P., Noelle, D. C., Braver, T. S., Cohen, J. D., and O'Reilly, R. (2005). Prefrontal cortex and flexible cognitive control: Rules without symbols. *Proceedings of the National Academy of Sciences*, **102**, 7338–7343.

Rowe, J. B., Sakai, K., Lund, T. E., Ramsøy, T., Christensen, M. S., Baare, W. F., et al. (2007). Is the prefrontal cortex necessary for establishing cognitive sets? *Journal of*

Neuroscience, **48**, 13303–13310.

Ruge, H., Braver, T., and Meiran, N. (2009). Attention, intention, and strategy in preparatory control. *Neuropsychologia*, **47**, 1670–1685.

Scangos, K. W., and Stuphorn, V. (2010). Medial frontal cortex motivates but does not control movement initiation in the countermanding task. *The Journal of Neuroscience*, **30**(5), 1968–1982.

Schiffer, A.-M., Waszak, F., and Yeung, N. (2015). The role of prediction and outcomes in adaptive cognitive control. *Journal of Physiology-Paris*, **109**(1–3), 38–52.

Scheffers, M. K., Coles, M. G. H., Bernstein, P., Gehring, W. J., and Donchin, E. (1996). Event-related brain potentials and error-related processing: An analysis of incorrect responses to go and no-go stimuli. *Psychophysiology*, **33**, 42–53.

Sellitto, M., Ciaramelli, E., and di Pellegrino, G. (2011). The neurobiology of intertemporal choice: Insight from imaging and lesion studies. *Reviews in the Neurosciences*, **22**(5), 565–574.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, Series B*, **298**(1089), 199–209.

Shallice, T., and Burgess, P. (1996). The domain of supervisory processes and temporal organization of behaviour. *Philosophical Transactions of the Royal Society of London Series B*, **351**, 1405–1411.

Shallice, T., and Evans, M. E. (1978). The involvement of frontal lobes in cognitive estimation. *Cortex*, **13**, 294–303.

Sharp, D. J., Bonnelle, V., de Boissezon, X., Beckmann, C. F., James, S. G., Patel, M. C., and Mehta, M. A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proceedings of the National Academy of*

Sciences, **107**(13), 6106–6111.

Shenhav, A., Botvinick, M. M., and Cohen, J. D. (2013). The expected value of control: An integrative theory of anterior cingulate cortex function. *Neuron*, **79**(2), 217–240.

Shibata, M., Abe, J., Terao, A., and Miyamoto, T. (2007). Neural mechanisms involved in the comprehension of metaphoric and literal sentences: An fMRI study. *Brain Research*, **1166**, 92–102.

Shiels, K., and Hawk, L. W. (2010). Self-regulation in ADHD: The role of error processing. *Clinical Psychology Review*, **30**(8), 951–961.

Silton, R. L., Heller, W., Towers, D. N., Engels, A. S., Spielberg, J. M., Edgar, J. C., et al. (2010). The time course of activity in dorsolateral prefrontal cortex and anterior cingulate cortex during top-down attentional control. *NeuroImage*, **50**(3), 1292–1302.

Slagter, H. A., Weissman, D. H., Giesbrecht, B., Kenemans, J. L., Mangun, G. R., Kok, A., and Woldorff, M. G. (2006). Brain regions activated by endogenous preparatory set-shifting as revealed by fMRI. *Cognitive, Affective, and Behavioral Neuroscience*, **6**(3), 175–189.

Smith, M. L., and Milner, B. (1984). Differential effects of frontal-lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia*, **22**, 697–705.

Soon, C. S., He, A. H., Bode, S., and Haynes, J.-D. (2013). Predicting free choices for abstract intentions. *Proceedings of the National Academy of Sciences*, **110**, 6217–6222.

Spencer, K. M., Dien, J., and Donchin, E. (1999). A componential analysis of the ERP elicited by novel events using a dense electrode array. *Psychophysiology*, **36**(3), 409–414.

Sprecht, K., Lie, C. H., Shah, N. J., and Fink, G. R. (2009). Disentangling the prefrontal network for rule selection by means of a non-verbal variant of the Wisconsin Card

Sorting Test. *Human Brain Mapping*, **30**, 1734–1743.

Stuss, D. T. (2011). Functions of the frontal lobes: Relation to executive functions. *Journal of the International Neuropsychological Society*, **17**(5), 759–765.

Stuss, D. T., and Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society of London, Series B*, **362**, 901–915.

Stuss, D. T., and Benson, D. F. (1986). *The frontal lobes*. New York: Raven Press.

Swick, D., Ashley, V., and Turken, U. (2011). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *NeuroImage*, **56**(3), 1655–1665.

Tallon-Baudry, C., and Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Science*, **3**, 151–162.

Tayeb, Y., and Lavidor, M. (2016). Enhancing switching abilities: Improving practice effect by stimulating the dorsolateral pre-frontal cortex. *Neuroscience*, **313**, 92–98.

Taylor, S. F., Martis, B., Fitzgerald, K. D., Welsh, R. C., Abelson, J. L., Liberzon, I., et al. (2006). Medial frontal cortex activity and loss-related responses to errors. *Journal of Neuroscience*, **26**(15), 4063–4070.

Taylor, S. F., Stern, E. R., and Gehring, W. J. (2007). Neural systems for error monitoring: Recent findings and theoretical perspectives. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, **13**(2), 160–172.

Thompson-Schill, S. L., Ramscar, M., and Chrysikou, E. G. (2009). Cognition without control: When a little frontal lobe goes a long way. *Current Directions in Psychological Science*, **18**, 259–263.

Thothathiri, M., Gagliardi, M., and Schwartz, M. F. (2012). Subdivision of frontal

cortex mechanisms for language production in aphasia. *Neuropsychologia*, **50**(14), 3284–3294.

Thothathiri, M., and Rattinger, M. (2015). Controlled processing during sequencing. *Frontiers in Human Neuroscience*, **9**, 599. <http://doi.org/10.3389/fnhum.2015.00599>

Ullsperger, M., Fischer, A. G., Nigbur, R., and Endrass, T. (2014). Neural mechanisms and temporal dynamics of performance monitoring. *Trends in Cognitive Sciences*, **18**(5), 259–267.

Ullsperger, M., Harsay, H. A., Wessel, J. R., and Ridderinkhof, K. R. (2010). Conscious perception of errors and its relation to the anterior insula. *Brain Structure and Function*, **214**, 629–643.

Unterrainer, J., Rahm, B., Kaller, C., Quiske, K., Hoppe-Seyler, K., Meier, C., et al. (2004). Planning abilities and the Tower of London: Is this task measuring a discrete cognitive function? *Journal of Clinical and Experimental Neuropsychology*, **26**, 846–856.

van Noordt, S. J. R., and Segalowitz, S. J. (2012). Performance monitoring and the medial prefrontal cortex: A review of individual differences and context effects as a window on self-regulation. *Frontiers in Human Neuroscience*, **6**, 197.

Wager, T. D., Jonides, J., Smith, E. E., and Nichols, T. E. (2005). Toward a taxonomy of attention shifting: Individual differences in fMRI during multiple shift types. *Cognitive, Affective and Behavioral Neuroscience*, **5**, 127–143.

Wagner, G., Koch, K., Reichenbach, J. R., Sauer, H., and Schlösser, R. G. (2006). The special involvement of the rostrolateral prefrontal cortex in planning abilities: An event-related fMRI study with the Tower of London paradigm. *Neuropsychologia*, **44**, 2337–2347.

Walton, M. E., Bannerman, D. M., Alterescu, K., and Rushworth, M. F. S. (2003).

Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. *The Journal of Neuroscience*, **23**(16), 6475–6479.

Wendelken, C., and Bunge, S. A. (2010). Transitive inference: Distinct contributions of rostrolateral prefrontal cortex and the hippocampus. *Journal of Cognitive Neuroscience*, **22**, 837–847.

Wessel, J. R., and Aron, A. R. (2017). On the globality of motor suppression: Unexpected events and their influence on behavior and cognition. *Neuron*, **93**(2), 259–280.

Whitmer, A. J., and Banich, M. T. (2012). Brain activity related to the ability to inhibit previous task sets: an fMRI study. *Cognitive, Affective and Behavioral Neuroscience*, **12**(4), 661–670.

Witt, S. T., and Stevens, M. C. (2012). Overcoming residual interference in mental set switching: Neural correlates and developmental trajectory. *NeuroImage*, **62**(3), 2055–2064.

van den Heuvel, O. A., Groenewegen, H. J., Barkhof, F., Lazeron, R. H., van Dyck, R., and Veltman, D. J. (2003). Frontostriatal system in planning complexity: A parametric functional magnetic resonance version of Tower of London Task. *NeuroImage*, **18**, 367–374.

Yamaguchi, S., and Knight, R. T. (1991). Anterior and posterior association cortex contributions to the somatosensory P300. *Journal of Neuroscience*, **11**, 2039–2054.

Yin, S., Wang, T., Pan, W., Liu, Y., and Chen, A. (2015). Task-switching cost and intrinsic functional connectivity in the human brain: Toward understanding individual differences in cognitive flexibility. *PLoS ONE*, **10**(12), e0145826.

Zarr, N., and Brown, J. W. (2016). Hierarchical error representation in medial prefrontal cortex. *NeuroImage*, **124**(Pt. A), 238–247.

Chapter 12

Adolphs, R., Cahill, L., Schul, R., and Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning and Memory*, **4**, 291–300.

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., and Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, **433**, 68–72.

Adolphs, R., Tranel, D., and Damasio, A. R. (1998). The human amygdala in social judgment. *Nature*, **393**, 470–474.

Adolphs, R., Tranel, D., and Damasio, H. (2001). Emotion recognition from faces and prosody following temporal lobectomy. *Neuropsychology*, **15**, 396–404.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, **37**, 1111–1117.

Aggleton, J. P., and Young, A. W. (2000). The enigma of the amygdala: On its contribution to human emotion. In R. D. Lane and L. Nadel (eds.), *Cognitive neuroscience of emotion* (pp. 106–128). New York: Oxford University Press.

Aharon, I., Etcoff, N., Ariely, D., Chabris, C. F., O'Connor, E., and Breiter, H. C. (2001). Beautiful faces have variable reward value: fMRI and behavioral evidence. *Neuron*, **32**, 537–551.

Alexander, W. H., and Brown, J. W. (2011). Medial prefrontal cortex as an action-outcome predictor. *Nature Neuroscience*, **14**, 1338–1344.

Alkire, M. T., Gruver, R., Miller, J., McReynolds, J. R., Hahn, E. L., and Cahill, L. (2008). Neuroimaging analysis of an anesthetic gas that blocks human emotional

memory. *Proceedings of the National Academy of Sciences*, **105**, 1722–1727.

Allman, J. M., Hakeem, A., Erwin, J. M., Nimchinsky, E., and Hof, P. (2001). The anterior cingulate cortex: The evolution of an interface between emotion and cognition. In A. R. Damasio, A. Harrington, J. Kagan, B. S. McEwen, H. Moss, and R. Shaikh (eds.), *Unity of knowledge: The convergence of natural and human science*. *Annals of the New York Academy of Sciences*, Vol. 935 (pp. 107–117). New York: The New York Academy of Sciences.

Allman, J. M., Tetreault, N. A., Hakeem, A. Y., and Park, S. (2011). The von Economo neurons in apes and humans. *American Journal of Human Biology*, **23**, 5–21.

Amodio, D. M. (2014). The neuroscience of prejudice and stereotyping. *Nature Reviews Neuroscience*, **15**, 670–682.

Amodio, D. M., Harmon-Jones, E., Devine, P. G., Curtin, J. J., Hartley, S. L., and Covert, A. E. (2004). Neural signals for the detection of unintentional race bias. *Psychological Science*, **15**, 88–93.

Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., et al. (2003). Dissociated neural representations of intensity and valence in human olfaction. *Nature Neuroscience*, **6**, 196–202.

Anderson, A. K., and Phelps, E. A. (2001). Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*, **411**, 305–309.

Anderson, A. K., and Phelps, E. A. (2002). Is the human amygdala critical for the subjective experience of emotion? Evidence of intact dispositional affect in patients with amygdala lesions. *Journal of Cognitive Neuroscience*, **14**, 709–720.

Anderson, N. E., and Kiehl, K. A. (2012). The psychopath magnetized: Insights from brain imaging, *Trends in Cognitive Sciences*, **16**, 52–60.

Armony, J. L., and LeDoux, J. E. (2000). How danger is encoded: Toward a systems, cellular, and computational understanding of cognitive-emotional interactions in fear. In M. S. Gazzaniga (ed.), *The new cognitive neurosciences* (pp. 1067–1079). Cambridge, MA: MIT Press.

Arnsten, A. F. (2015). Stress weakens prefrontal networks: Molecular insults to higher cognition. *Nature Neuroscience*, **18**(10), 1376–1385.

Aubé, W., Angulo-Perkins, A., Peretz, I., Concha, L., and Armony, J. L. (2015). Fear across the senses: Brain responses to music, vocalizations and facial expressions. *Social Cognitive and Affective Neuroscience*, **10**, 399–407.

Baliki, M. N., Mansour, A., Baria, A. T., Huang, L., Berger, S. E., Fields, H. L., and Apkarian, A. V. (2013). Parceling human accumbens into putative core and shell dissociates encoding of values for reward and pain. *Journal of Neuroscience*, **33**, 16383–16393.

Bar-Haim, Y. (2010). Research review: Attention bias modification (ABM): A novel treatment for anxiety disorders. *Journal of Child Psychology and Psychiatry*, **51**, 859–870.

Barrett, F. S., and Janata, P. (2016). Neural responses to nostalgia-evoking music modeled by elements of dynamic musical structure and individual differences in affective traits. *Neuropsychologia*, **91**, 234–246.

Bauernfeind, A. L., de Sousa, A. A., Avasthi, T., Dobson, S. D., Raghanti, M. A., Lewandowski, A. H., Hof, P. R., et al. (2013). A volumetric comparison of the insular cortex and its subregions in primates. *Journal of Human Evolution*, **64**, 263–279.

Baxter, M. G., and Murray, E. A. (2002). The amygdala and reward. *Nature Reviews Neuroscience*, **3**, 563–573.

Beauregard, M., Levesque, J., and Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *Journal of Neuroscience*, **21**(18), RC165(1–6).

Bechara, A., Damasio, A. R., Damasio, H., and Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, **50**, 7–15.

Bechara, A., Damasio, H., and Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, **10**, 295–307.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., and Damasio, R. A. R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, **269**(5227), 1115–1118.

Beckmann, M., Johansen-Berg, H., and Rushworth, M. F. S. (2009). Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization. *Journal of Neuroscience*, **29**, 1175–1190.

Belyk, M., and Brown, S. (2014). Perception of affective and linguistic prosody: An ALE meta-analysis of neuroimaging studies. *Social Cognitive and Affective Neuroscience*, **9**, 1395–1403.

Berns, G. S., McClure, S. M., Pagnoni, G., and Montague, P. R. (2001). Predictability modulates human brain response to reward. *Journal of Neuroscience*, **21**, 2793–2798.

Berridge, K. C. (2003). Pleasures of the brain. *Brain and Cognition*, **5**, 106–128.

Berridge, K. C., and Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, **28**, 309–369.

Berridge, K. C., and Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, **26**, 507–513.

Blair, R. J. R., Morris, J. S., Frith, C. D., Perrett, D. I., and Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, **122**, 883–893.

Browning, M., Holmes, E. A., Murphy, S. E., Goodwin, G. M., and Harmer, C. J. (2010). Lateral prefrontal cortex mediates the cognitive modification of attentional bias. *Biological Psychiatry*, **67**, 919–925.

Buchanan, T. W., Lutz, K., Mirzazade, S., Specht, K., Shah, N. J., Zilles, K., and Jancke, L. (2000). Recognition of emotional prosody and verbal components of spoken language: An fMRI study. *Cognitive Brain Research*, **9**, 227–238.

Büchel, C., Bornhøvd, K., Qunata, M., Glauche, V., Bromm, B., and Weiler, C. (2002). Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: A parametric single-trial laser functional magnetic resonance imaging study. *Journal of Neuroscience*, **22**, 970–976.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Ochsner, K. N., et al. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex*, **24**, 2981–2990.

Bumiller, E. (1982, March 31). Jim Brady's long ordeal. *Washington Post*.

Bush, G., Luu, P., and Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, **4**, 215–222.

Buss, K. A., Schumacher, J. R. M., Dolski, I., Kalin, N. H., Goldsmith, H. H., and Davidson, R. J. (2003). Right frontal brain activity, cortisol, and withdrawal behavior in 6-month-old infants. *Behavioral Neuroscience*, **117**, 11–20.

Calder, A. J., Keane, J., Manes, F., Antoun, N., and Young, A. W. (2000). Impaired recognition and experience of disgust following brain injury. *Nature Neuroscience*, **3**,

1077–1078.

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., and Etcoff, N. L. (1996). Facial emotion recognition after bilateral amygdala damage: Differentially severe impairment of fear. *Cognitive Neuropsychology*, **13**, 699–745.

Camille, N., Coricelli, G., Sallet, J., Pradat-Diehl, P., Duhamel, J.-R., and Sirigu, A. (2004). The involvement of the orbitofrontal cortex in the experience of regret. *Science*, **304**, 1167–1170.

Castro, D. C., and Berridge, K. C. (2014). Advances in the neurobiological bases for food “liking” versus “wanting.” *Physiology and Behavior*, **136**, 22–30.

Chang, L. J., Yarkoni, T., Khaw, M. W., and Sanfey, A. G. (2013). Decoding the role of the insula in human cognition: Functional parcellation and large-scale reverse inference. *Cerebral Cortex*, **23**, 739–749.

Chapman, H. A., Kim, D. A., Susskind, J. M., and Anderson, A. K. (2009). In bad taste: Evidence for the oral origins of moral disgust. *Science*, **323**, 1222–1226.

Coan, J. A., and Allen, J. J. B. (2004). Frontal EEG asymmetry as a moderator and mediator of emotion. *Biological Psychology*, **67**, 7–49.

Cohen, R. A., Kaplan, R. F., Zuffante, P., Moser, D. J., Jenkins, M. A., Salloway, S., and Wilkinson, H. (1999). Alteration of intention and self-initiated action associated with bilateral anterior cingulotomy. *Journal of Neuropsychiatry and Clinical Neurosciences*, **11**, 444–453.

Compton, R. J. (2003). The interface between emotion and attention: A review of evidence from psychology and neuroscience. *Behavioral and Cognitive Neuroscience Reviews*, **2**, 115–129.

Coricelli, G., Critchley, H. D., Joffily, M., O'Doherty, J. P., Sirigu, A., and Dolan, R. J.

(2005). Regret and its avoidance: A neuroimaging study of choice behavior. *Nature Neuroscience*, **8**, 1255–1262.

Correia, S. S., and Goosens, K. A. (2016). Input-specific contributions to valence processing in the amygdala. *Learning and Memory*, **23**, 534–543.

Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience*, **3**, 655–666.

Craig, A. D. (2009). How do you feel – now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, **10**, 59–70.

Critchley, H. D., Rotshtein, P., Öhman, A., and Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, **7**, 189–195.

Critchley, H. D., Tang, J., Glaser, D., Butterworth, B., and Dolan, R. J. (2005). Anterior cingulate activity during error and autonomic response. *NeuroImage*, **27**, 885–895.

Cytowic, R. E. (1981, September 27). The long ordeal of James Brady. *New York Times*.

Damasio, A. R. (1994). *Descartes' error: Emotion, reason, and the human brain*. New York: Avon Books.

Darwin, C. (1873/1965). *The expression of the emotions in man and animals*. Chicago: University of Chicago Press.

David, S. P., Munafo, M. R., Johansen-Berg, H., Smith, S. M., Rogers, R. D., Matthews, P. M., and Walton, R. T. (2005). Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: A functional magnetic resonance imaging study. *Biological Psychiatry*, **58**, 488–494.

Davidson, R. J. (2004). What does the prefrontal cortex “do” in affect: Perspectives on

frontal EEG asymmetry research. *Biological Psychology*, **67**, 219–233.

Davidson, R. J., Ekman, P., Saron, C. D., Senulis, J. A., and Friesen, W. V. (1990). Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology I. *Journal of Personality and Social Psychology*, **58**, 330–341.

Davidson, R. J., and Fox, N. A. (1989). Frontal brain asymmetry predicts infants' response to maternal separation. *Journal of Abnormal Psychology*, **98**, 127–131.

Deen, B., Pitskel, N. B., and Pelphrey, K. A. (2011). Three systems of insular functional connectivity identified with cluster analysis. *Cerebral Cortex*, **21**, 1498–1506.

de la Vega, A., Chang, L. J., Banich, M. T., Wager, T. D., and Yarkoni, T. (2016). Large-scale meta-analysis of human medial frontal cortex reveals tripartite functional organization. *Journal of Neuroscience*, **36**, 6553–6562.

Denny, B. T., Inhoff, M. C., Zerubavel, N., Davachi, L., and Ochsner, K. N. (2015). Getting over it: Long-lasting effects of emotion regulation on amygdala response. *Psychological Science*, **26**, 1377–1388.

Depue, B. E., Curran, T., and Banich, M. T. (2007). Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. *Science*, **317**, 215–219.

De Witt, K. (1990, December 18). James Brady relives the day he became a symbol. *New York Times*.

Dolan, R. J., and Morris, J. S. (2000). The functional anatomy of innate and acquired fear: Perspectives from neuroscience. In R. D. Lane and L. Nadel (eds.), *Cognitive neuroscience of emotion* (pp. 156–191). New York: Oxford University Press.

Drevets, W. C., and Raichle, M. E. (1998). Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implications for interaction between emotion and cognition. *Cognition and Emotion*, **12**, 353–385.

Ekman, P., Sorenson, E. R., and Friesen, W. V. (1969). Pan-cultural elements in facial displays of emotion. *Science*, **164**, 86–88.

Elfenbein, H. A., and Ambady, N. (2002). On the universality and cultural specificity of emotion recognition: A meta-analysis. *Psychological Bulletin*, **128**, 203–235.

Ellsworth, P. C. (1994). William James and emotion: Is a century of fame worth a century of misunderstanding? *Psychological Review*, **101**, 222–229.

Etkin, A., Egner, T., and Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, **15**, 85–93.

Evrard, H. C., Forro, T., and Logothetis, N. K. (2012). Von Economo neurons in the anterior insula of the macaque monkey. *Neuron*, **74**, 482–489.

Feeser, M., Prehn, K., Kazzer, P., Mungee, A., and Bajbouj, M. (2014). Transcranial direct current stimulation enhances cognitive control during emotion regulation. *Brain Stimulation*, **7**, 105–112.

Feinstein, J. S., Buzza, C., Hurlemann, R., Follmer, R. L., Dahdaleh, N. S., Coryell, W. H., Wemmie, J. A., et al. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature Neuroscience*, **16**, 270–272.

Feldman-Barrett, L., and Russell, J. A. (1999). The structure of current affect: Controversies and emerging consensus. *Current Directions in Psychological Science*, **8**, 10–14.

Fernandez-Carriba, S., Loeches, A., Morcillo, A., and Hopkins, W. D. (2002). Asymmetry in facial expression of emotions by chimpanzees. *Neuropsychologia*, **40**, 1523–1533.

Fiorillo, C. D., Tobler, P. N., and Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. *Science*, **299**, 1898–1902.

Floresco, S. B. (2015). The nucleus accumbens: An interface between cognition, emotion, and action. *Annual Review of Psychology*, **66**, 25–52.

Foti, D., and Hajcak, G. (2008). Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. *Journal of Cognitive Neuroscience*, **20**, 977–988.

Fox, N. A., and Davidson, R. J. (1986). Taste-elicited changes in facial signs of emotion and the asymmetry of brain electrical activity in human newborns. *Neuropsychologia*, **24**, 417–422.

Freese, J. L., and Amaral, D. G. (2009). Neuroanatomy of the primate amygdala. In P. J. Whalen and E. A. Phelps (eds.), *The human amygdala* (pp. 3–42). New York: Guilford.

Gendron, M., Roberson, D., van der Vyver, J. M., and Barrett, L. F. (2014). Perceptions of emotion from facial expressions are not culturally universal: Evidence from a remote culture. *Emotion*, **14**, 251–262.

Gosselin, N., Paquette, S., and Peretz, I. (2015). Sensitivity to musical emotions in congenital amusia. *Cortex*, **71**, 171–182.

Gosselin, N., Peretz, I., Johnsen, E., and Adolphs, R. (2007). Amygdala damage impairs emotion recognition from music. *Neuropsychologia*, **45**, 236–244.

Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, **2**, 271–299.

Gross, J. J. (2013). Emotion regulation: Taking stock and moving forward. *Emotion*, **13**, 359–365.

Gu, X., Hof, P. R., Friston, K. J., and Fan, J. (2013). Anterior insular cortex and emotional awareness. *Journal of Comparative Neurology*, **521**, 3371–3388.

Hadj-Bouziane, F., Liu, N., Bell, A. H., Gothard, K. M., Luh, W. M., Tootell, R. B., Ungerleider, L. G., et al. (2012). Amygdala lesions disrupt modulation of functional MRI activity evoked by facial expression in the monkey inferior temporal cortex. *Proceedings of the National Academy of Sciences*, **109**, E3640–E3648.

Hadland, K. A., Rushworth, M. F. S., Gaffan, D., and Passingham, R. E. (2003). The effect of cingulate lesions on social behaviour and emotion. *Neuropsychologia*, **41**, 919–931.

Hajcak, G., and Foti, D. (2008). Errors are aversive: Defensive motivation and the error-related negativity. *Psychological Science*, **19**, 103–108.

Hajcak, G., and Nieuwenhuis, S. (2006). Reappraisal modulates the electrocortical response to unpleasant pictures. *Cognitive, Affective, and Behavioral Neuroscience*, **6**, 291–297.

Harmon-Jones, E. (2004). Contributions from research on anger and cognitive dissonance to understanding the motivational functions of asymmetrical brain activity. *Biological Psychology*, **67**, 51–76.

Harmon-Jones, E. (2007). Trait anger predicts relative left frontal cortical activation to anger-inducing stimuli. *International Journal of Psychophysiology*, **66**, 154–160.

Hauser, M. (1993). Right hemisphere dominance in the production of facial expression in monkeys. *Science*, **261**, 475–477.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology*, **7**, 476–489.

Heller, W., Koven, N. S., and Miller, G. A. (2003). Regional brain activity in anxiety and depression, cognition/emotion interaction, and emotion regulation. In K. Hugdahl and R. J. Davidson (eds.), *The asymmetrical brain* (pp. 533–564). Cambridge, MA:

MIT Press.

Heller, W., and Nitschke, J. B. (1998). The puzzle of regional brain activity in depression and anxiety: The importance of subtypes and comorbidity. *Cognition and Emotion*, **12**, 421–447.

Hennenlotter, A., and Schroeder, U. (2006). Partly dissociable neural substrates for recognizing basic emotions: A critical review. *Progress in Brain Research*, **156**, 443–456.

Hollerman, J. R., and Schultz, W. (1998). Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience*, **1**, 304–309.

Holroyd, C. B., and Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, **109**, 679–709.

Inzlicht, M., Bartholow, B. D., and Hirsh, J. B. (2015). Emotional foundations of cognitive control. *Trends in Cognitive Sciences*, **19**, 126–132.

Inzlicht, M., and Gutsell, J. N. (2007). Running on empty: Neural signals for self-control failure. *Psychological Science*, **18**, 933–937.

Jabbi, M., Bastiaansen, J., and Keysers, C. (2008). A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity patterns. *PLoS ONE*, **3**, e2939.

James, W. (1884). What is an emotion? *Mind*, **9**, 188–205.

Kahnt, T., Heinzle, J., Park, S. Q., and Haynes, J.-D. (2010). The neural code of reward anticipation in human orbitofrontal cortex. *Proceedings of the National Academy of Sciences*, **107**, 6010–6015.

Kalin, N. H., Larson, C., Shelton, S. E., and Davidson, R. J. (1998). Asymmetric frontal brain activity, cortisol, and behavior associated with fearful temperament in rhesus monkeys. *Behavioral Neuroscience*, **112**, 286–292.

Kalin, N. H., Shelton, S. E., and Davidson, R. J. (2000). Cerebrospinal fluid corticotropin-releasing hormone levels are elevated in monkeys with patterns of brain activity associated with a fearful temperament. *Biological Psychiatry*, **47**, 579–585.

Kalisch, R., Wiech, K., Critchley, H. D., Seymour, B., O'Doherty, J. P., Oakley, D. A., et al. (2005). Anxiety reduction through detachment: Subjective, physiological, and neural effects. *Journal of Cognitive Neuroscience*, **17**, 874–883.

Kampe, K. K. W., Frith, C. D., Dolan, R. J., and Frith, U. (2001). Reward value of attractiveness and gaze. *Nature*, **413**, 589.

Kawasaki, H., Tsuchiya, N., Kovach, C. K., Nourski, K. V., Oya, H., Howard, M. A., and Adolphs, R. (2012). Processing of facial emotion in the human fusiform gyrus. *Journal of Cognitive Neuroscience*, **24**, 1358–1370.

Klüver, H., and Bucy, P. C. (1937). “Psychic blindness” and other symptoms following bilateral temporal lobectomy in rhesus monkeys. *American Journal of Physiology*, **119**, 352–353.

Knutson, B., Adams, C. M., Fong, G. W., and Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, **21**, RC159(1–5).

Knutson, B., Westdorp, A., Kaiser, E., and Hommer, D. (2000). fMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*, **12**, 20–27.

Koelsch, S. (2014). Brain correlates of music-evoked emotions. *Nature Reviews Neuroscience*, **15**, 170–180.

Kragel, P. A., Knodt, A. R., Hariri, A. R., and LaBar, K. S. (2016). Decoding spontaneous emotional states in the human brain. *PLoS Biology*, **14**, e2000106.

Kringelbach, M. L. (2005). The human orbitofrontal cortex: Linking reward to hedonic experience. *Nature Reviews Neuroscience*, **6**, 691–702.

Kringelbach, M. L., O'Doherty, J., Rolls, E. T., and Andrews, C. (2003). Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral Cortex*, **13**, 1064–1071.

Krompinger, J. W., Moser, J. S., and Simons, R. F. (2008). Modulations of the electrophysiological response to pleasant stimuli by cognitive reappraisal. *Emotion*, **8**, 132–137.

Larson, C. L., Schaefer, H. S., Siegle, G. J., Jackson, C. A. B., Anderle, M. J., and Davidson, R. J. (2006). Fear is fast in phobic individuals: Amygdala activation in response to fear-relevant stimuli. *Biological Psychiatry*, **60**, 410–417.

LeDoux, J. (1996). *The emotional brain: The mysterious underpinnings of emotional life*. New York: Touchstone.

LeDoux, J. E. (2014). Coming to terms with fear. *Proceedings of the National Academy of Sciences*, **111**, 2871–2878.

Livneh, U., and Paz, R. (2012). Amygdala-prefrontal synchronization underlies resistance to extinction of aversive memories. *Neuron*, **75**, 133–142.

Machado, C. J., Kazama, A. M., and Bachevalier, J. (2009). Impact of amygdala, orbital frontal, or hippocampal lesions on threat avoidance and emotional reactivity in nonhuman primates. *Emotion*, **9**, 147–163.

MacLean, P. D. (1949). Psychosomatic disease and the “visceral brain”: Recent developments’ bearing on the Papez theory of emotion. *Psychosomatic Medicine*, **11**,

338–353.

MacLean, P. D. (1952). Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalography and Clinical Neurophysiology*, **4**, 407–418.

Marsh, A. A., Elfenbein, H. A., and Ambady, N. (2003). Nonverbal “accents”: Cultural differences in facial expressions of emotion. *Psychological Science*, **14**, 373–376.

Matsumoto, D., Yoo, S. H., Hiramaya, S., and Petrova, G. (2005). Development and validation of a measure of display-rule knowledge: The display rule assessment inventory. *Emotion*, **5**, 23–40.

Matthews, S. C., Paulus, M. P., Simmons, A. N., Nelesen, R. A., and Dimsdale, J. E. (2004). Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *NeuroImage*, **22**, 1151–1156.

McGinley, J. J., and Friedman, B. H. (2015). Autonomic responses to lateralized cold pressor and facial cooling tasks. *Psychophysiology*, **52**, 416–424.

McManus, I. C., and Humphrey, N. K. (1973). Turning the left cheek. *Nature*, **243**, 271–272.

Michl, P., Meindl, T., Meister, F., Born, C., Engel, R. R., Reiser, M., and Hennig-Fast, K. (2014). Neurobiological underpinnings of shame and guilt: A pilot fMRI study. *Social Cognitive and Affective Neuroscience*, **9**, 150–157.

Mitchell, R. L., and Ross, E. D. (2013). Attitudinal prosody: What we know and directions for future study. *Neuroscience and Biobehavioral Reviews*, **37**, 471–479.

Mohanty, A., Engels, A. S., Herrington, J. D., Heller, W., Ho, M.-H. R., Banich, M. T., et al. (2007). Differential engagement of anterior cingulate cortex subdivisions for cognitive and emotional function. *Psychophysiology*, **44**, 343–351.

Monrad-Krohn, G. H. (1947). Dysprosody of altered “melody of language.” *Brain*, **70**, 405–415.

Montreys, C. R., and Borod, J. C. (1998). A preliminary evaluation of emotional experience and expression following unilateral brain damage. *International Journal of Neuroscience*, **96**, 269–283.

Murray, E. A. (2007). The amygdala, reward, and emotion. *Trends in Cognitive Sciences*, **11**, 489–497.

Nicholls, M. E. R., Clode, D., Wood, S. J., and Wood, A. G. (1999). Laterality of expression in portraiture: Putting your best cheek forward. *Proceedings of the Royal Society of London, Series B*, **266**, 1517–1522.

Niedenthal, P. M. (2007). Embodying emotion. *Science*, **316**, 1002–1005.

Norman-Haignere, S., Kanwisher, N. G., and McDermott, J. H. (2015). Distinct cortical pathways for music and speech revealed by hypothesis-free voxel decomposition. *Neuron*, **88**, 1281–1296.

Ochsner, K. N., Bunge, S. A., Gross, J. J., and Gabrieli, J. D. E. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, **14**, 1215–1229.

Ochsner, K. N., Silvers, J. A., and Buhle, J. T. (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, **1251**, E1–E24.

O’Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., and Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience*, **4**, 95–102.

Olds, J., and Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*, **47**, 419–427.

Olsson, A., and Phelps, E. A. (2007). Social learning of fear. *Nature Neuroscience*, **10**, 1095–1102.

Padoa-Schioppa, C. (2011). Neurobiology of economic choice: A good-based model. *Annual Review of Neuroscience*, **34**, 333–359.

Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurological Psychiatry*, **38**, 725–743.

Paz, R., and Pare, D. (2013). Physiological basis for emotional modulation of memory circuits by the amygdala. *Current Opinion in Neurobiology*, **23**, 381–386.

Pell, M. D. (1999). Fundamental frequency encoding of linguistic and emotional prosody by right hemisphere-damaged speakers. *Brain and Language*, **69**, 161–192.

Pell, M. D. (2006). Cerebral mechanisms for understanding emotional prosody in speech. *Brain and Language*, **96**, 221–234.

Peltola, M. J., Bakermans-Kranenburg, M. J., Alink, L. R., Huffmeijer, R., Biro, S., and van IJzendoorn, M. H. (2014). Resting frontal EEG asymmetry in children: Meta-analyses of the effects of psychosocial risk factors and associations with internalizing and externalizing behavior. *Developmental Psychobiology*, **56**, 1377–1389.

Penfield, W., and Faulk, M. E. (1955). The insula: Further observations on its function. *Brain*, **78**, 445–470.

Pessoa, L. (2010). Emotion and cognition and the amygdala: from “what is it?” to “what’s to be done?” *Neuropsychologia*, **48**, 3416–3429.

Pessoa, L., and Adolphs, R. (2011). Emotion and the brain: Multiple roads are better than one. *Nature Reviews Neuroscience*, **12**, 425.

Pessoa, L., and Pereira, M. G. (2013). Cognition-emotion interactions. In M. D. Robinson, E. R. Watkins, and E. Harmon-Jones (eds.), *Handbook of cognition and emotion*. New York: Guilford Press.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., and Tancer, M. E. (2006). Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biological Psychiatry*, **59**, 424–429.

Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Current Opinion in Neurobiology*, **14**, 198–202.

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Gore, J. C., Grillon, C., and Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nature Neuroscience*, **4**, 437–441.

Raio, C. M., Orederu, T. A., Palazzolo, L., Shurick, A. A., and Phelps, E. A. (2013). Cognitive emotion regulation fails the stress test. *Proceedings of the National Academy of Sciences*, **110**, 15139–15144.

Roberts, A. C. (2006). Primate orbitofrontal cortex and adaptive behaviour. *Trends in Cognitive Sciences*, **10**, 83–90.

Robinson, M. J., Fischer, A. M., Ahuja, A., Lesser, E. N., and Maniates, H. (2015). Roles of “wanting” and “liking” in motivating behavior: Gambling, food, and drug addictions. *Current Topics in Behavioral Neurosciences*, 1–32.

Rolls, E. T. (1999). *The brain and emotion*. Oxford: Oxford University Press.

Rolls, E. T. (2015). Limbic systems for emotion and for memory, but no single limbic system. *Cortex*, **62**, 119–157.

Rolls, E. T., Hornak, J., Wade, D., and McGrath, J. (1994). Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology, Neurosurgery, and Psychiatry*, **57**, 1518–1524.

Ross, E. D. (2006). The aprosodias. In M. J. Farah and T. E. Feinberg (eds.), *Patient-based approaches to cognitive neuroscience* (2nd edn.). Cambridge, MA: MIT Press.

Ross, E. D. (2013). Affective prosody. In D. B. Arciniegas, C. A. Anderson, and C. M. Filley (eds.), *Behavioral neurology and neuropsychiatry*. Cambridge: Cambridge University Press.

Ross, E. D., and Monnot, M. (2008). Neurology of affective prosody and its functional-anatomic organization in right hemisphere. *Brain and Language*, **104**, 51–74.

Ross, E. D., and Pulusu, V. K. (2013). Posed versus spontaneous facial expressions are modulated by opposite cerebral hemispheres. *Cortex*, **49**, 1280–1291.

Rushworth, M., Buckley, M., Behrens, T., Walton, M., and Bannerman, D. (2007). Functional organization of the medial frontal cortex. *Current Opinion in Neurobiology*, **17**, 220–227.

Saarimäki, H., Gotsopoulos, A., Jääskeläinen, I. P., Lampinen, J., Vuilleumier, P., Hari, R., Nummenmaa, L., et al. (2016). Discrete neural signatures of basic emotions. *Cerebral Cortex*, **26**, 2563–2573.

Sackeim, H. A., Gur, R. C., and Saucy, M. C. (1978). Emotions are expressed more intensely on the left side of the face. *Science*, **202**, 434.

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., and Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nature Neuroscience*, **14**, 257–262.

Salimpoor, V. N., van den Bosch, I., Kovacevic, N., McIntosh, A. R., Dagher, A., and

Zatorre, R. J. (2013). Interactions between the nucleus accumbens and auditory cortices predict music reward value. *Science*, **340**, 216–219.

Salimpoor, V. N., Zald, D. H., Zatorre, R. J., Dagher, A., and McIntosh, A. R. (2015). Predictions and the brain: How musical sounds become rewarding. *Trends in Cognitive Sciences*, **19**, 86–91.

Schaffer, C. E., Davidson, R. J., and Saron, C. (1983). Frontal and parietal electroencephalogram asymmetry in depressed and nondepressed subjects. *Biological Psychiatry*, **18**, 753–762.

Schienle, A., Schafer, A., and Vaitl, D. (2008). Individual differences in disgust imagery: A functional magnetic resonance imaging study. *NeuroReport*, **19**, 527–530.

Sergerie, K., Chochol, C., and Armony, J. L. (2008). The role of the amygdala in emotional processing: A quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, **32**, 811–830.

Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., and Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience*, **12**, 154–167.

Shankman, S. A., Klein, D. N., Tenke, C. E., and Bruder, G. E. (2007). Reward sensitivity in depression: A biobehavioral study. *Journal of Abnormal Psychology*, **116**, 95–104.

Shin, L. M., Dougherty, D. D., Orr, S. P., Pitman, R. K., Lasko, M., Macklin, M. L., et al. (2000). Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biological Psychiatry*, **48**, 43–50.

Small, D. M., Gregory, M. D., Mak, Y. E., Gitelman, D., Mesulam, M. M., and Parrish, T. (2003). Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron*, **39**, 701–711.

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., and Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate: From pleasure to aversion. *Brain*, **124**, 1720–1733.

Stalnaker, T. A., Cooch, N. K., and Schoenbaum, G. (2015). What the orbitofrontal cortex does not do. *Nature Neuroscience*, **18**, 620–627.

Stark, R., Zimmerman, M., Kagerer, S., Schienle, A., Walter, B., Weygandt, M., and Vaitl, D. (2007). Hemodynamic brain correlates of disgust and fear ratings. *NeuroImage*, **37**, 663–673.

Steiner, A. P., and Redish, A. D. (2014). Behavioral and neurophysiological correlates of regret in rat decision-making on a neuroeconomic task. *Nature Neuroscience*, **17**, 995–1002.

Sutton, S. K. (2002). Incentive and threat reactivity: Relations with anterior cortical activity. In D. Cervone and W. Mischel (eds.), *Advances in personality science* (pp. 127–150). New York: Guilford Press.

Tanabe, J., Reynolds, J., Krmpotich, T., Claus, E., Thompson, L. L., Du, Y. P., and Banich, M. T. (2013). Reduced neural tracking of prediction error in substance-dependent individuals. *The American Journal of Psychiatry*, **170**, 1356–1363.

Taylor, K. S., Seminowicz, D. A., and Davis, K. D. (2009). Two systems of resting state connectivity between the insula and cingulate cortex. *Human Brain Mapping*, **30**, 2731–2745.

Thibodeau, R., Jorgensen, R. S., and Kim, S. (2006). Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology*, **115**, 715–729.

Tomer, R., Slagter, H. A., Christian, B. T., Fox, A. S., King, C. R., Murali, D.,

Davidson, R. J., et al. (2014). Love to win or hate to lose? Asymmetry of dopamine D2 receptor binding predicts sensitivity to reward versus punishment. *Journal of Cognitive Neuroscience*, **26**, 1039–1048.

Touroutoglou, A., Lindquist, K. A., Dickerson, B. C., and Barrett, L. F. (2015). Intrinsic connectivity in the human brain does not reveal networks for “basic” emotions. *Social Cognitive and Affective Neuroscience*, **10**, 1257–1265.

Tracey, I. (2005). Nocioceptive processing in the human brain. *Current Opinion in Neurobiology*, **15**, 478–487.

Tranel, D., Damasio, A., and Damasio, H. (1988). Intact recognition of facial expression, gender, and age in patients with impaired recognition of face identity. *Neurology*, **38**, 690–696.

Tucker, D. M., Watson, R. T., and Heilman, K. M. (1977). Discrimination and evocation of affectively intoned speech in patients with right parietal disease. *Neurology*, **27**, 947–958.

Uddin, L. Q., Kinnison, J., Pessoa, L., and Anderson, M. L. (2014). Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *Journal of Cognitive Neuroscience*, **26**, 16–27.

van Lancker, D., and Sidtis, J. J. (1992). The identification of affective-prosodic stimuli by left and right brain damaged subjects: All errors are not created equal. *Journal of Speech and Hearing Research*, **35**, 963–970.

Verhagen, J. V. (2007). The neurocognitive bases of human multimodal food perception: Consciousness. *Brain Research Reviews*, **53**, 271–286.

Vuilleumier, P. (2005). How brains beware: Neural mechanisms of emotional attention. *Trends in Cognitive Sciences*, **9**, 585–594.

Walker, J. P., Daigle, T., and Buzzard, M. (2002). Hemispheric specialization in processing prosodic structures: Revisited. *Aphasiology*, **16**, 1155–1172.

Wallez, C., and Vauclair, J. (2012). First evidence of population-level oro-facial asymmetries during the production of distress calls by macaque (*Macaca mulatta*) and baboon (*Papio anubis*) infants. *Behavioural Brain Research*, **234**, 69–75.

Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science*, **306**, 2061.

Wittling, W., Block, A., Schweiger, E., and Genzel, S. (1998). Hemisphere asymmetry in sympathetic control of the human myocardium. *Brain and Cognition*, **38**, 17–35.

Wittling, W., and Pflüger, M. (1990). Neuroendocrine hemisphere asymmetries: Salivary cortisol secretion during lateralized viewing of emotion-related and neutral films. *Brain and Cognition*, **14**, 243–265.

Woolley, J. D., Strobl, E. V., Sturm, V. E., Shany-Ur, T., Poorzand, P., Grossman, S., Miller, B. L., et al. (2015). Impaired recognition and regulation of disgust is associated with distinct but partially overlapping patterns of decreased gray matter volume in the ventroanterior insula. *Biological Psychiatry*, **78**, 505–514.

Xu, X., Zuo, X., Wang, X., and Han, S. (2009). Do you feel my pain? Racial group membership modulates empathic neural responses. *Journal of Neuroscience*, **29**, 8525–8529.

Yonelinas, A. P., and Ritchey, M. (2015). The slow forgetting of emotional episodic memories: An emotional binding account. *Trends in Cognitive Sciences*, **19**, 259–267.

Young, A. W., Newcombe, F., de Haan, E. H. F., Small, M., and Hay, D. C. (1993). Face perception after brain injury: Selective impairments affecting identity and expression. *Brain*, **116**, 941–959.

Chapter 13

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th edn.). Washington, DC: Author.

Amodio, D. M. (2014). The neuroscience of prejudice and stereotyping. *Nature Reviews Neuroscience*, **15**, 670–682.

Amodio, D. M., Devine, P. G., and Harmon-Jones, E. (2007). A dynamic model of guilt: Implications for motivation and self-regulation in the context of prejudice. *Psychological Science*, **18**, 524–530.

Amodio, D. M., Harmon-Jones, E., Devine, P. G., Curtin, J. J., Hartley, S. L., and Covert, A. E. (2004). Neural signals for the detection of unintentional race bias. *Psychological Science*, **15**, 88–93.

Amodio, D. M., Kubota, J. T., Harmon-Jones, E., and Devine, P. G. (2006). Alternative mechanisms for regulating racial responses according to internal vs external cues. *Social Cognitive and Affective Neuroscience*, **1**, 26–36.

Asch, S. E. (1951). Effects of group pressure upon the modification and distortion of judgments. In H. Guetzkow (ed.), *Groups, leadership and men: Research in human relations* (pp. 177–190). Pittsburgh: Carnegie Press.

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O’Riordan, M., and Bullmore, E. T. (2007). Differential activation of the amygdala and the “social brain” during fearful face-processing in Asperger syndrome. *Neuropsychologia*, **45**, 2–14.

Bach, D. R., Hurlemann, R., and Dolan, R. J. (2015). Impaired threat prioritisation after selective bilateral amygdala lesions. *Cortex*, **63**, 206–213.

Baron-Cohen, S., Leslie, A. M., and Frith, U. (1985). Does the autistic child have a “theory of mind”? *Cognition*, **21**, 37–46.

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., and Williams, S. C. (1999). Social intelligence in the normal and autistic brain: An fMRI study. *European Journal of Neuroscience*, **11**, 1891–1898.

Batson, C. D. (2009). These things called empathy: Eight related but distinct phenomena. In J. Decety and W. Ickers (eds.), *The social neuroscience of empathy*. Cambridge, MA: MIT Press.

Beer, J. S., John, O. P., Scabini, D., and Knight, R. T. (2006). Orbitofrontal cortex and social behavior: Integrating self-monitoring and emotion-cognition interactions. *Journal of Cognitive Neuroscience*, **18**, 871–879.

Berridge, K. C., and Kringelbach, M. L. (2015). Pleasure systems in the brain. *Neuron*, **86**(3), 646–664.

Bickart, K. C., Brickhouse, M., Negreira, A., Sapolsky, D., Barrett, L. F., and Dickerson, B. C. (2014). Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale. *Journal of Neurology, Neurosurgery and Psychiatry*, **85**, 438–448.

Blair, R. J. R. (2005). Responding to the emotions of others: Dissociating forms of empathy through the study of typical and psychiatric populations. *Consciousness and Cognition*, **14**, 698–718.

Borod, J. C., Cicero, B. A., Obler, L. K., Welkowitz, J., Erhan, H. M., Santschi, C., et al. (1998). Right hemisphere emotional perception: Evidence across multiple channels. *Neuropsychology*, **12**, 446–458.

Brescoll, V., and LaFrance, M. (2004). The correlates and consequences of newspaper reports of research on sex differences. *Psychological Science*, **15**, 515–520.

Brüne, M., and Brüne-Cohrs, U. (2006). Theory of mind – evolution, ontogeny, brain

mechanisms and psychopathology. *Neuroscience and Biobehavioral Reviews*, **30**, 437–455.

Campbell-Meiklejohn, D. K., Bach, D. R., Roepstorff, A., Dolan, R. J., and Frith, C. D. (2010). How the opinion of others affects our valuation of objects. *Current Biology*, **20**, 1165–1170.

Campbell-Meiklejohn, D. K., Simonsen, A., Jensen, M., Wohler, V., Gjerløff, T., Scheel-Kruger, J., Roepstorff, A., et al. (2012). Modulation of social influence by methylphenidate. *Neuropsychopharmacology*, **37**, 1517–1525.

Carp, J., Halenar, M., Quandt, L. C., Sklar, A., and Compton, R. J. (2009). Perceived similarity and neural mirroring: Evidence from vicarious error processing. *Social Neuroscience*, **4**, 85–96.

Carter, R. M., and Huettel, S. A. (2013). A nexus model of the temporal–parietal junction. *Trends in Cognitive Sciences*, **17**, 328–336.

Castelli, F., Frith, C., Happé, F., and Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain*, **125**, 1839–1849.

Castelli, F., Happé, F., Frith, U., and Frith, C. (2000). Movement and mind: A functional imaging study of perception and interpretation of complex intentional movement patterns. *Neuroimage*, **12**, 314–325.

Channon, S., Drury, H., Gafson, L., Stern, J., and Robertson, M. M. (2012). Judgements of social inappropriateness in adults with Tourette's syndrome. *Cognitive Neuropsychiatry*, **17**, 246–261.

Chartrand, T. L., and Lakin, J. L. (2013). The antecedents and consequences of human behavioral mimicry. *Annual Review of Psychology*, **64**, 285–308.

Chen, K. H., Rusch, M. L., Dawson, J. D., Rizzo, M., and Anderson, S. W. (2015). Susceptibility to social pressure following ventromedial prefrontal cortex damage. *Social Cognitive and Affective Neuroscience*, e-publication ahead of print.

Cialdini, R. B., and Goldstein, N. J. (2004). Social influence: Compliance and conformity. *Annual Review of Psychology*, **55**, 591–621.

Cikara, M., Botvinick, M. M., and Fiske, S. T. (2011). Us versus them: Social identity shapes neural responses to intergroup competition and harm. *Psychological Science*, **22**, 306–313.

Cook, R., Bird, G., Catmur, C., Press, C., and Heyes, C. (2014). Mirror neurons: From origin to function. *Behavioral and Brain Sciences*, **37**, 177–192.

Correll, J., Park, B., Judd, C. M., and Wittenbrink, B. (2002). The police officer's dilemma: Using ethnicity to disambiguate potentially threatening individuals. *Journal of Personality and Social Psychology*, **83**, 1314–1329.

Cunningham, W. A., Johnson, M. K., Raye, C. L., Gatenby, J. C., Gore, J. C., and Banaji, M. R. (2004). Separable neural components in the processing of black and white faces. *Psychological Science*, **15**, 806–813.

Dal Monte, O., Costa, V. D., Noble, P. L., Murray, E. A., and Averbeck, B. B. (2015). Amygdala lesions in rhesus macaques decrease attention to threat. *Nature communications*, **6**.

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., and Iacoboni, M. (2006). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, **9**, 28–30.

D'Argembeau, A., Feyers, D., Majerus, S., Collette, F., van der Linden, M., Maquet, P., and Salmon, E. (2008). Self-reflection across time: Cortical midline structures

differentiate between present and past selves. *Social Cognitive and Affective Neuroscience*, **3**, 244.

D'Argembeau, A., Stawarczyk, D., Majerus, S., Collette, F., van der Linden, M., and Salmon, E. (2010). Modulation of medial prefrontal and inferior parietal cortices when thinking about past, present, and future selves. *Social Neuroscience*, **5**, 187–200.

Dar-Nimrod, I., and Heine, S. J. (2006). Exposure to scientific theories affects women's math performance. *Science*, **314**, 435.

Denny, B. T., Kober, H., Wager, T. D., and Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self-and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience*, **24**, 1742–1752.

Derks, B., Inzlicht, M., and Kang, S. (2008). The neuroscience of stigma and stereotype threat. *Group Processes and Intergroup Relations*, **11**, 163–181.

Deschamps, P. K., Been, M., and Matthys, W. (2014). Empathy and empathy induced prosocial behavior in 6-and 7-year-olds with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, **44**, 1749–1758.

Di Pellegrino, G., Fadiga, L., Fogassi, L., Gallese, V., and Rizzolatti, G. (1992). Understanding motor events: A neurophysiological study. *Experimental Brain Research*, **91**, 176–180.

Dickter, C. L., and Bartholow, B. D. (2007). Racial ingroup and outgroup attention biases revealed by event-related brain potentials. *Social Cognitive and Affective Neuroscience*, **2**, 189–198.

Dunbar, R. I. (1992). Neocortex size as a constraint on group size in primates. *Journal of Human Evolution*, **22**, 469–493.

Dunbar, R. I. (2009). The social brain hypothesis and its implications for social evolution. *Annals of Human Biology*, **36**, 562–572.

Dunbar, R. I., and Shultz, S. (2007). Evolution in the social brain. *Science*, **317**, 1344–1347.

Dziobek, I., Rogers, K., Fleck, S., Bahnemann, M., Heekeren, H. R., Wolf, O. T., and Convit, A. (2008). Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). *Journal of Autism and Developmental Disorders*, **38**, 464–473.

Eisenberger, N. I., Lieberman, M. D., and Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science*, **302**, 290–292.

Ersner-Hersfield, H., Wimmer, G. E., and Knutson, B. (2009). Saving for the future self: Neural measures of future self-continuity predict temporal discounting. *Social Cognitive and Affective Neuroscience*, **4**, 85–92.

Flavell, J. H. (2004). Theory-of-mind development: Retrospect and prospect. *Merrill-Palmer Quarterly*, **50**(3), 274–290.

Forbes, C. E., and Leitner, J. B. (2014). Stereotype threat engenders neural attentional bias toward negative feedback to undermine performance. *Biological Psychology*, **102**, 98–107.

Forbes, C. E., Schmader, T., and Allen, J. J. (2008). The role of devaluing and discounting in performance monitoring: A neurophysiological study of minorities under threat. *Social Cognitive and Affective Neuroscience*, **3**, 253–261.

Fourie, M. M., Thomas, K. G., Amodio, D. M., Warton, C. M., and Meintjes, E. M. (2014). Neural correlates of experienced moral emotion: An fMRI investigation of emotion in response to prejudice feedback. *Social Neuroscience*, **9**, 203–218.

Gervais, H., Belin, P., Boddaert, N., Leboyer, M., Coez, A., Sfaello, I., et al. (2004). Abnormal cortical voice processing in autism. *Nature Neuroscience*, **7**, 801–802.

Gillihan, S. J., and Farah, M. J. (2005). Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. *Psychological Bulletin*, **131**, 76–97.

Golkar, A., Björnstjerna, M., and Olsson, A. (2015). Learned fear to social out-group members are determined by ethnicity and prior exposure. *Frontiers in Psychology*, **6**.

Gonzalez-Liencre, C., Shamay-Tsoory, S. G., and Brüne, M. (2013). Towards a neuroscience of empathy: Ontogeny, phylogeny, brain mechanisms, context and psychopathology. *Neuroscience and Biobehavioral Reviews*, **37**, 1537–1548.

Hadjikhani, N., Zürcher, N. R., Rogier, O., Hippolyte, L., Lemonnier, E., Ruest, T., Helles, A., et al. (2014). Emotional contagion for pain is intact in autism spectrum disorders. *Translational Psychiatry*, **4**, e343.

Hamilton, A. F. C., Brindley, R. M., and Frith, U. (2007). Imitation and action understanding in autistic spectrum disorders: How valid is the hypothesis of a deficit in the mirror neuron system? *Neuropsychologia*, **45**, 1859–1868.

Hamilton, A. F. D. C. (2013). Reflecting on the mirror neuron system in autism: A systematic review of current theories. *Developmental Cognitive Neuroscience*, **3**, 91–105.

Heider, F., and Simmel, M. (1944). An experimental study of apparent behavior. *The American Journal of Psychology*, 243–259.

Hein, G., Silani, G., Preuschoff, K., Batson, C. D., and Singer, T. (2010). Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. *Neuron*, **68**, 149–160.

Heiser, M., Iacoboni, M., Maeda, F., Marcus, J., and Mazziotta, J. C. (2003). The essential role of Broca's area in imitation. *European Journal of Neuroscience*, **17**, 1123–1128.

Hickok, G. (2013). Do mirror neurons subserve action understanding? *Neuroscience Letters*, **540**, 56–58.

Hogeveen, J., Obhi, S. S., Banissy, M. J., Santiesteban, I., Press, C., Catmur, C., and Bird, G. (2015). Task-dependent and distinct roles of the temporoparietal junction and inferior frontal cortex in the control of imitation. *Social Cognitive and Affective Neuroscience*, **10**, 1003–1009.

Iacoboni, M. (2009). Imitation, empathy, and mirror neurons. *Annual Review of Psychology*, **60**, 653–670.

Iacoboni, M., and Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nature Reviews Neuroscience*, **7**, 942–951.

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., and Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science*, **286**, 2526–2528.

Ito, T. (2011). Perceiving social category information from faces: Using ERPs to study person perception. In A. Todorov, S. T. Fiske, and D. A. Prentice (eds.), *Social neuroscience: Toward understanding the underpinnings of the social mind*. Oxford: Oxford University Press.

Ito, T. A., Friedman, N. P., Bartholow, B. D., Correll, J., Loersch, C., Altamirano, L. J., and Miyake, A. (2015). Toward a comprehensive understanding of executive cognitive function in implicit racial bias. *Journal of Personality and Social Psychology*, **108**, 187–218.

Ito, T. A., Thompson, E., and Cacioppo, J. T. (2004). Tracking the timecourse of social

perception: The effects of racial cues on event-related brain potentials. *Personality and Social Psychology Bulletin*, **30**, 1267–1280.

Jackson, P. L., Meltzoff, A. N., and Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. *Neuroimage*, **24**, 771–779.

Janak, P. H., and Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, **517**(7534), 284–292.

Jones, A. P., Happé, F. G., Gilbert, F., Burnett, S., and Viding, E. (2010). Feeling, caring, knowing: Different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, **51**, 1188–1197.

Jones, R. M., Somerville, L. H., Li, J., Ruberry, E. J., Libby, V., Glover, G., Casey, B. J., et al. (2011). Behavioral and neural properties of social reinforcement learning. *Journal of Neuroscience*, **31**, 13039–13045.

Kana, R. K., Wadsworth, H. M., and Travers, B. G. (2011). A systems level analysis of the mirror neuron hypothesis and imitation impairments in autism spectrum disorders. *Neuroscience and Biobehavioral Reviews*, **35**, 894–902.

Kent, R. G., Carrington, S. J., Couteur, A., Gould, J., Wing, L., Maljaars, J., R Leekam, S., et al. (2013). Diagnosing Autism Spectrum Disorder: Who will get a DSM-5 diagnosis? *Journal of Child Psychology and Psychiatry*, **54**, 1242–1250.

Kilner, J. M., Neal, A., Weiskopf, N., Friston, K. J., and Frith, C. D. (2009). Evidence of mirror neurons in human inferior frontal gyrus. *Journal of Neuroscience*, **29**, 10153–10159.

Kim, B. R., Liss, A., Rao, M., Singer, Z., and Compton, R. J. (2012). Social deviance activates the brain's error-monitoring system. *Cognitive, Affective, and Behavioral*

Neuroscience, **12**, 65–73.

Klauer, K. C., Schmitz, F., Teige-Mocigemba, S., and Voss, A. (2010). Understanding the role of executive control in the Implicit Association Test: Why flexible people have small IAT effects. *The Quarterly Journal of Experimental Psychology*, **63**, 595–619.

Klin, A., Jones, W., Schultz, R., Volkmar, F., and Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, **59**, 809–816.

Klucharev, V., Hytönen, K., Rijpkema, M., Smidts, A., and Fernández, G. (2009). Reinforcement learning signal predicts social conformity. *Neuron*, **61**, 140–151.

Klucharev, V., Munneke, M. A., Smidts, A., and Fernández, G. (2011). Downregulation of the posterior medial frontal cortex prevents social conformity. *Journal of Neuroscience*, **31**, 11934–11940.

Krendl, A. C., Richeson, J. A., Kelley, W. M., and Heatherton, T. F. (2008). The negative consequences of threat: An fMRI investigation of the neural mechanisms underlying women's underperformance in math. *Psychological Science*, **19**, 168–175.

Krienen, F. M., Tu, P. C., and Buckner, R. L. (2010). Clan mentality: Evidence that the medial prefrontal cortex responds to close others. *Journal of Neuroscience*, **30**, 13906–13915.

Kubota, J. T., Banaji, M. R., and Phelps, E. A. (2012). The neuroscience of race. *Nature Neuroscience*, **15**(7), 940–948.

Kulage, K. M., Smaldone, A. M., and Cohn, E. G. (2014). How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *Journal of Autism and Developmental Disorders*, **44**, 1918–1932.

Lakin, J. L., and Chartrand, T. L. (2003). Using nonconscious behavioral mimicry to

create affiliation and rapport. *Psychological Science*, **14**, 334–339.

Lakin, J. L., Chartrand, T. L., and Arkin, R. M. (2008). I am too just like you: Nonconscious mimicry as an automatic behavioral response to social exclusion. *Psychological Science*, **19**, 816–822.

Langford, D. J., Crager, S. E., Shehzad, Z., Smith, S. B., Sotocinal, S. G., Levenstadt, J. S., Mogil, J. S., et al. (2006). Social modulation of pain as evidence for empathy in mice. *Science*, **312**, 1967–1970.

Leighton, J., Bird, G., Orsini, C., and Heyes, C. (2010). Social attitudes modulate automatic imitation. *Journal of Experimental Social Psychology*, **46**, 905–910.

Leopold, A., Krueger, F., dal Monte, O., Pardini, M., Pulaski, S. J., Solomon, J., and Grafman, J. (2012). Damage to the left ventromedial prefrontal cortex impacts affective theory of mind. *Social Cognitive and Affective Neuroscience*, **7**, 871–880.

MacDonald, G., and Leary, M. R. (2005). Why does social exclusion hurt? The relationship between social and physical pain. *Psychological Bulletin*, **131**, 202–223.

Mangels, J. A., Good, C., Whiteman, R. C., Maniscalco, B., and Dweck, C. S. (2012). Emotion blocks the path to learning under stereotype threat. *Social Cognitive and Affective Neuroscience*, **7**, 230–241.

Maren, S., Phan, K. L., and Liberzon, I. (2013). The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, **14**(6), 417–428.

Meyer, M. L., Masten, C. L., Ma, Y., Wang, C., Shi, Z., Eisenberger, N. I., and Han, S. (2013). Empathy for the social suffering of friends and strangers recruits distinct patterns of brain activation. *Social Cognitive and Affective Neuroscience*, **8**, 446–454.

Mobbs, D., Yu, R., Meyer, M., Passamonti, L., Seymour, B., Calder, A. J., Schweizer,

S., Frith, C. D., and Dalglish, T. (2009). A key role for similarity in vicarious reward. *Science*, **324**, 900.

Moran, J. M., Jolly, E., and Mitchell, J. P. (2014). Spontaneous mentalizing predicts the fundamental attribution error. *Journal of Cognitive Neuroscience*, **26**, 569–576.

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., and Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. *Current Biology*, **20**, 750–756.

Neal, D. T., and Chartrand, T. L. (2011). Embodied emotion perception: Amplifying and dampening facial feedback modulates emotion perception accuracy. *Social Psychological and Personality Science*, **2**, 673–678.

Nosek, B. A., Hawkins, C. B., and Frazier, R. S. (2011). Implicit social cognition: From measures to mechanisms. *Trends in Cognitive Sciences*, **15**, 152–159.

Oberman, L. M., and Ramachandran, V. S. (2007). The simulating social mind: The role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychological Bulletin*, **133**, 310–327.

Ogden, J. A. (2005). *Fractured minds: A case-study approach to clinical neuropsychology* (2nd edn.). Oxford: Oxford University Press.

Olsson, A., Ebert, J. P., Banaji, M. R., and Phelps, E. A. (2005). The role of social groups in the persistence of learned fear. *Science*, **309**, 785–787.

Panksepp, J., and Panksepp, J. B. (2013). Toward a cross-species understanding of empathy. *Trends in Neurosciences*, **36**, 489–496.

Payne, B. K. (2005). Conceptualizing control in social cognition: How executive functioning modulates the expression of automatic stereotyping. *Journal of Personality and Social Psychology*, **89**, 488–503.

Pelphrey, K. A., Morris, J. P., and McCarthy, G. (2005). Neural basis of eye gaze processing deficits in autism. *Brain*, **128**, 1038–1048.

Pessoa, L., and Adolphs, R. (2010). Emotion processing and the amygdala: From a “low road” to “many roads” of evaluating biological significance. *Nature Reviews Neuroscience*, **11**(11), 773–783.

Phelps, E. A., Cannistraci, C. J., and Cunningham, W. A. (2003). Intact performance on an indirect measure of race bias following amygdala damage. *Neuropsychologia*, **41**, 203–208.

Phelps, E. A., O'Connor, K. J., Cunningham, W. A., Funayama, E. S., Gatenby, J. C., Gore, J. C., and Banaji, M. R. (2000). Performance on indirect measures of race evaluation predicts amygdala activation. *Journal of Cognitive Neuroscience*, **12**, 729–738.

Pichon, S., and Kell, C. A. (2013). Affective and sensorimotor components of emotional prosody generation. *Journal of Neuroscience*, **33**(4), 1640–1650.

Pierce, K. A., Müller, R.-A., Ambrose, J., Allen, G., and Courchesne, E. (2001). Face processing occurs outside the fusiform “face area” in autism: Evidence from functional MRI. *Brain*, **124**, 2059–2073.

Povinelli, D. J., and Vonk, J. (2003). Chimpanzee minds: Suspiciously human? *Trends in Cognitive Sciences*, **7**, 157–160.

Rameson, L. T., Morelli, S. A., and Lieberman, M. D. (2012). The neural correlates of empathy: Experience, automaticity, and prosocial behavior. *Journal of Cognitive Neuroscience*, **24**, 235–245.

Ratner, K. G., and Amodio, D. M. (2013). Seeing “us vs. them”: Minimal group effects on the neural encoding of faces. *Journal of Experimental Social Psychology*, **49**,

298–301.

Ratner, K. G., Kaul, C., and van Bavel, J. J. (2013). Is race erased? Decoding race from patterns of neural activity when skin color is not diagnostic of group boundaries. *Social Cognitive and Affective Neuroscience*, **8**, 750–755.

Rogers, K., Dziobek, I., Hassenstab, J., Wolf, O. T., and Convit, A. (2007). Who cares? Revisiting empathy in Asperger syndrome. *Journal of Autism and Developmental Disorders*, **37**, 709–715.

Ross, L. (1977). The intuitive psychologist and his shortcomings: Distortions in the attribution process. In L. Berkowitz (ed.), *Advances in experimental social psychology* (pp. 173–220). New York: Academic Press.

Ruff, C. C., Ugazio, G., and Fehr, E. (2013). Changing social norm compliance with noninvasive brain stimulation. *Science*, **342**, 482–484.

Sacks, O. (1995). *An anthropologist on Mars: Seven paradoxical tales*. New York: Alfred A. Knopf.

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., and Cohen, J. D. (2003). The neural basis of economic decision-making in the ultimatum game. *Science*, **300**, 1755–1758.

Sanfey, A. G., Stallen, M., and Chang, L. J. (2014). Norms and expectations in social decision-making. *Trends in Cognitive Sciences*, **18**(4), 172–174.

Saxe, R., and Kanwisher, N. (2003). People thinking about thinking people: The role of the temporo-parietal junction in “theory of mind.” *Neuroimage*, **19**, 1835–1842.

Schmader, T., Johns, M., and Forbes, C. (2008). An integrated process model of stereotype threat effects on performance. *Psychological Review*, **115**, 336–356.

Schnuerch, R., and Gibbons, H. (2014). A review of neurocognitive mechanisms of social conformity. *Social Psychology*, **45**(6), 466–478.

Schnuerch, R., and Gibbons, H. (2015). Social proof in the human brain: Electrophysiological signatures of agreement and disagreement with the majority. *Psychophysiology*, **52**(10), 1328–1342.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., and Perner, J. (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. *Neuroscience and Biobehavioral Reviews*, **42**, 9–34.

Senholzi, K. B., Depue, B. E., Correll, J., Banich, M. T., and Ito, T. A. (2015). Brain activation underlying threat detection to targets of different races. *Social Neuroscience*, **10**, 651–662.

Silk, J. B. (2007). Social components of fitness in primate groups. *Science*, **317**, 1347–1351.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, **303**, 1157–1162.

Somerville, L. H., Heatherton, T. F., and Kelley, W. M. (2006). Anterior cingulate cortex responds differentially to expectancy violation and social rejection. *Nature Neuroscience*, **9**, 1007–1008.

Spezio, M. L., Adolphs, R., Hurley, R. S. E., and Piven, J. (2007). Analysis of face gaze in autism using “Bubbles.” *Neuropsychologia*, **45**, 144–151.

Spikman, J. M., Timmerman, M. E., Milders, M. V., Veenstra, W. S., and van der Naalt, J. (2012). Social cognition impairments in relation to general cognitive deficits, injury severity, and prefrontal lesions in traumatic brain injury patients. *Journal of*

Neurotrauma, **29**, 101–111.

Spitzer, M., Fischbacher, U., Herrnberger, B., Grön, G., and Fehr, E. (2007). The neural signature of social norm compliance. *Neuron*, **56**, 185–196.

Stallen, M., and Sanfey, A. G. (2015). The neuroscience of social conformity: Implications for fundamental and applied research. *Frontiers in Neuroscience*, **9**.

Steele, C. M., and Aronson, J. (1995). Stereotype threat and the intellectual test performance of African Americans. *Journal of Personality and Social Psychology*, **69**, 797–811.

Stel, M., and van Knippenberg, A. (2008). The role of facial mimicry in the recognition of affect. *Psychological Science*, **19**, 984–985.

Tajfel, H. (1970). Experiments in intergroup discrimination. *Scientific American*, **223**, 96–102.

Toelch, U., and Dolan, R. J. (2015). Informational and normative influences in conformity from a neurocomputational perspective. *Trends in Cognitive Sciences*, **19**, 579–589.

Tomasello, M., Call, J., and Hare, B. (2003). Chimpanzees understand psychological states – the question is which ones and to what extent. *Trends in Cognitive Sciences*, **7**, 153–156.

Tsai, L. Y., and Ghaziuddin, M. (2014). DSM-5 ASD moves forward into the past. *Journal of Autism and Developmental Disorders*, **44**, 321–330.

van Bavel, J. J., Packer, D. J., and Cunningham, W. A. (2008). The neural substrates of in-group bias: A functional magnetic resonance imaging investigation. *Psychological Science*, **19**, 1131–1139.

van Schie, H. T., Mars, R. B., Coles, M. G. H., and Bekkering, H. (2004). Modulation of activity in medial frontal and motor cortices during error observation. *Nature Neuroscience*, **7**, 549–554.

von dem Hagen, E. A., Stoyanova, R. S., Rowe, J. B., Baron-Cohen, S., and Calder, A. J. (2014). Direct gaze elicits atypical activation of the theory-of-mind network in autism spectrum conditions. *Cerebral Cortex*, **24**, 1485–1492.

Wagner, D. D., Haxby, J. V., and Heatherton, T. F. (2012). The representation of self and person knowledge in the medial prefrontal cortex. *Wiley Interdisciplinary Reviews: Cognitive Science*, **3**, 451–470.

Walter, H. (2012). Social cognitive neuroscience of empathy: Concepts, circuits, and genes. *Emotion Review*, **4**, 9–17.

Wang, Y., Newport, R., and Hamilton, A. F. D. C. (2011a). Eye contact enhances mimicry of intransitive hand movements. *Biology Letters*, **7**, 7–10.

Wang, Y., Ramsey, R., and Hamilton, A. F. D. C. (2011b). The control of mimicry by eye contact is mediated by medial prefrontal cortex. *Journal of Neuroscience*, **31**, 12001–12010.

White, S., Hill, E., Happé, F., and Frith, U. (2009). Revisiting the strange stories: Revealing mentalizing impairments in autism. *Child Development*, **80**, 1097–1117.

Wicker, B., Keysers, C., Plailly, J., Royet, J., Gallese, V., and Rizzolatti, G. (2003). Both of us disgusted in my insula: The common neural basis of seeing and feeling disgust. *Neuron*, **40**, 655–664.

Woo, C. W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., Wager, T. D., et al. (2014). Separate neural representations for physical pain and social rejection. *Nature Communications*, **5**, 5380.

Wraga, M., Helt, M., Jacobs, E., and Sullivan, K. (2007). Neural basis of stereotype-induced shifts in women's mental rotation performance. *Social Cognitive and Affective Neuroscience*, **2**, 12–19.

Xu, X., Zuo, X., Wang, X., and Han, S. (2009). Do you feel my pain? Racial group membership modulates empathic neural responses. *Journal of Neuroscience*, **29**, 8525–8529.

Zaki, J., and Ochsner, K. N. (2012). The neuroscience of empathy: Progress, pitfalls and promise. *Nature Neuroscience*, **15**, 675–680.

Zaki, J., Weber, J., Bolger, N., and Ochsner, K. (2009). The neural bases of empathic accuracy. *Proceedings of the National Academy of Sciences*, **106**, 11382–11387.

Zilbovicious, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y., and Boddaert, N. (2006). Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences*, **29**, 359–366.

Chapter 14

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th edn.). Washington, DC: American Psychiatric Association.

Anderson, R. J., Frye, M. A., Abulseoud, O. A., Lee, K. H., McGillivray, J. A., Berk, M., and Tye, S. J. (2012). Deep brain stimulation for treatment-resistant depression: Efficacy, safety and mechanisms of action *Neuroscience and Biobehavioral Reviews*, **36**, 1920–1933.

Andreasen, N. C., Liu, D., Ziebell, S., Vora, A., and Ho, B. C. (2013). Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: A prospective longitudinal MRI study. *The American Journal of Psychiatry*, **170**, 609–615.

Andrews, G., and Titov, N. (2007). Depression is very disabling. *Lancet*, **370**, 808–809.

Armstrong, T., and Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. *Clinical Psychology Review*, **32**, 704–723.

Avery, D. H., Holtzheimer, P. E., Fawaz, W., Russo, J., Neumaier, J., Dunner, D. L., et al. (2006). A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biological Psychiatry*, **59**, 187–194.

Badiani, A., Belin, D., Epstein, D., Calu, D., and Shaham, Y. (2011). Opiate versus psychostimulant addiction: The differences do matter. *Nature Reviews Neuroscience*, **12**, 685–700.

Bähner, F., and Meyer-Lindenberg, A. (2017). Hippocampal–prefrontal connectivity as a translational phenotype for schizophrenia. *European Neuropsychopharmacology*, **27**(2), 93–106.

Banca, P., Voon, V., Vestergaard, M. D., Philipiak, G., Almeida, I., Pocinho, F., Castelo-Branco, M., et al. (2015). Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder. *Brain*, **138**(3), 798–811.

Banks, G. P., Mikell, C. B., Youngerman, B. E., Henriques, B., Kelly, K. M., Chan, A. K., Sheth, S. A., et al. (2015). Neuroanatomical characteristics associated with response to dorsal anterior cingulotomy for obsessive-compulsive disorder. *JAMA Psychiatry*, **72**, 127–135.

Barahona-Corrêa, J. B., Camacho, M., Castro-Rodrigues, P., Costa, R., and Oliveira-Maia, A. J. (2015). From thought to action: How the interplay between neuroscience and phenomenology changed our understanding of obsessive-compulsive disorder. *Frontiers in Psychology*, **6**.

Barch, D. M. (2005). The cognitive neuroscience of schizophrenia. *Annual Review of Clinical Psychology*, **1**, 321–353.

Barch, D. M., and Ceaser, A. (2012). Cognition in schizophrenia: Core psychological and neural mechanisms. *Trends in Cognitive Sciences*, **16**, 27–34.

Barch, D. M., Csernansky, J. G., Conturo, T., and Snyder, A. Z. (2002). Working and long-term memory deficits in schizophrenia: Is there a common prefrontal mechanism? *Journal of Abnormal Psychology*, **111**, 478–494.

Barry, T. J., Sewart, A. R., Arch, J. J., and Craske, M. G. (2015). Deficits in disengaging attention from threat predict improved response to cognitive behavioral therapy for anxiety. *Depression and Anxiety*, **32**(12), 892–899.

Bechara, A., and Damasio, H. (2002). Decision-making and addiction (Part I): Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia*, **40**, 1675–1689.

Beevers, C. G., Gibb, B. E., McGeary, J. E., and Miller, I. W. (2007). Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *Journal of Abnormal Psychology*, **116**, 208–212.

Behar, E., Zellig, A. R., and Borkovec, T. D. (2005). Thought and imaginal activity during worry and trauma recall. *Behavior Therapy*, **36**, 157–168.

Berry, S. M., Broglio, K., Bunker, M., Jayewardene, A., Olin, B., and Rush, A. J. (2013). A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. *Medical Devices (Auckland, NZ)*, **6**, 17.

Berton, O., and Nestler, E. J. (2006). New drug approaches to antidepressant drug discovery: Beyond monoamines. *Nature Reviews Neuroscience*, **7**, 137–151.

Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: An integrative account. *Trends in Cognitive Sciences*, **11**, 307–316.

Bishop, S. J., Duncan, J., Brett, M., and Lawrence, A. D. (2004a). Prefrontal cortical function and anxiety: Controlling attention to threat-related stimuli. *Nature Neuroscience*, **7**, 184–188.

Bishop, S. J., Duncan, J., and Lawrence, A. D. (2004b). State anxiety modulation of the amygdala response to unattended threat-related stimuli. *Journal of Neuroscience*, **24**, 10364–10368.

Bittner, R. A., Linden, D. E., Roebroek, A., Härtling, F., Rotarska-Jagiela, A., Maurer, K., Haenschel, C., et al. (2015). The when and where of working memory dysfunction in early-onset schizophrenia – a functional magnetic resonance imaging study. *Cerebral Cortex*, **25**, 2494–2506.

Bohlken, M. M., Brouwer, R. M., Mandl, R. C., van den Heuvel, M. P., Hedman, A. M., de Hert, M., Pol, H. E. H., et al. (2016). Structural brain connectivity as a genetic

marker for schizophrenia. *JAMA Psychiatry*, **73**, 11–19.

Boileau, I., Dagher, A., Leyton, M., Welfeld, K., Booij, L., Diksic, M., and Benkelfat, C. (2007). Conditioned dopamine release in humans: A positron emission tomography ¹¹[C]raclopride study with amphetamine. *Journal of Neuroscience*, **27**, 3998–4003.

Bossert, J. M., Stern, A. L., Theberge, F. R., Cifani, C., Koya, E., Hope, B. T., and Shaham, Y. (2011). Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. *Nature Neuroscience*, **14**, 420–422.

Braff, D. L. (2004). Psychophysiological and information processing approaches to schizophrenia. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (2nd edn.) (pp. 324–338). Oxford: Oxford University Press.

Braff, D. L., and Light, G. A. (2004). Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology*, **174**, 75–85.

Brambilla, P., Cerini, R., Gasparini, A., Versace, A., Andreone, N., Vittorini, E., et al. (2005). Investigation of corpus callosum in schizophrenia with diffusion imaging. *Schizophrenia Research*, **79**, 201–210.

Brent, B. K., Thermenos, H. W., Keshavan, M. S., and Seidman, L. J. (2013). Gray matter alterations in schizophrenia high-risk youth and early-onset schizophrenia: A review of structural MRI findings. *Child and Adolescent Psychiatric Clinics of North America*, **22**(4), 689–714.

Brett, Z. H., Humphreys, K. L., Smyke, A. T., Gleason, M. M., Nelson, C. A., Zeanah, C. H., Drury, S. S., et al. (2015). Serotonin transporter linked polymorphic region (5-HTTLPR) genotype moderates the longitudinal impact of early caregiving on externalizing behavior. *Development and Psychopathology*, **27**, 7–18.

Brody, A. L., Mandelkern, M. A., London, E. D., Childress, A. R., Lee, G. S., Bota, R. G., et al. (2002). Brain metabolic changes during cigarette craving. *Archives of*

General Psychiatry, **59**, 1162–1172.

Brown, L. T., Mikell, C. B., Youngerman, B. E., Zhang, Y., McKhann, G. M., and Sheth, S. A. (2016). Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: A systematic review of observational studies. *Journal of Neurosurgery*, **124**, 77–89.

Bruder, G. E., Tenke, C. E., Warner, V., Nomura, Y., Grillon, C., Hille, J., et al. (2005). Electroencephalographic measures of regional hemispheric activity in offspring at risk for depressive disorders. *Biological Psychiatry*, **57**, 328–335.

Bruder, G. E., Tenke, C. E., Warner, V., and Weissman, M. M. (2007). Grandchildren at high and low risk for depression differ in EEG measures of regional brain asymmetry. *Biological Psychiatry*, **62**, 1317–1323.

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., Loo, C. K., et al. (2016). Transcranial direct current stimulation for acute major depressive episodes: Meta-analysis of individual patient data. *British Journal of Psychiatry*, **208**, 522.

Buchsbaum, M. S., Friedman, J., Buchsbaum, B. R., Chu, K.-W., Hazlett, E. A., Newmark, R., et al. (2006). Diffusion tensor imaging in schizophrenia. *Biological Psychiatry*, **60**, 1181–1187.

Burdwood, E. N., Infantolino, Z. P., Crocker, L. D., Spielberg, J. M., Banich, M. T., Miller, G. A., and Heller, W. (2016). Resting-state functional connectivity differentiates anxious apprehension and anxious arousal. *Psychophysiology*, **53**, 1451–1459.

Burke, H. M., Davis, M. C., Otte, C., and Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*, **30**, 846–856.

Calhoun, G. G., and Tye, K. M. (2015). Resolving the neural circuits of anxiety. *Nature*

Neuroscience, **18**, 1394–1404.

Canli, T., and Lesch, K.-P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience*, **10**, 1103–1109.

Caspi, A., Sugden, K., Moffit, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, **301**, 386–389.

Cavedini, P., Gorini, A., and Bellodi, L. (2006). Understanding obsessive-compulsive disorder: Focus on decision-making. *Neuropsychology Review*, **16**, 3–15.

Chamberlain, S. R., Blackwell, A. D., Fineberg, N. A., Robbins, T. W., and Sahakian, B. J. (2005). The neuropsychology of obsessive-compulsive disorder: The importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience and Biobehavioral Reviews*, **29**, 399–419.

Chase, H. W., Eickhoff, S. B., Laird, A. R., and Hogarth, L. (2011). The neural basis of drug stimulus processing and craving: An activation likelihood estimation meta-analysis. *Biological Psychiatry*, **70**, 785–793.

Chavarria-Siles, I., White, T., de Leeuw, C., Goudriaan, A., Lips, E., Ehrlich, S., Ho, B. C., et al. (2016). Myelination-related genes are associated with decreased white matter integrity in schizophrenia. *European Journal of Human Genetics*, **24**, 381–386.

Christian, K. M., Song, H., and Ming, G. L. (2014). Functions and dysfunctions of adult hippocampal neurogenesis. *Annual Review of Neuroscience*, **37**, 243–262.

Cisler, J. M., and Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*, **30**, 203–216.

Clark, L., Chamberlain, S. R., and Sahakian, B. J. (2009). Neurocognitive mechanisms in depression: Implications for treatment. *Annual Review of Neuroscience*, **32**, 57–74.

Crombag, H. S., Gorny, G., Li, Y., Kolb, B., and Robinson, T. E. (2005). Opposite effects of amphetamine self-administration experience on dendritic spines in the medial and orbital prefrontal cortex. *Cerebral Cortex*, **15**, 341–348.

C'urc'i'c-Blake, B., Liemburg, E., Vercammen, A., Swart, M., Knegtering, H., Bruggeman, R., and Aleman, A. (2013). When Broca goes uninformed: Reduced information flow to Broca's area in schizophrenia patients with auditory hallucinations. *Schizophrenia Bulletin*, **39**, 1087–1095.

Dalglish, M. R. C., Weinstein, A., Malizia, A. L., Wilson, S., Melichar, J. K., Britten, S., et al. (2001). Changes in regional cerebral blood flow elicited by craving memories in abstinent opiate-dependent subjects. *American Journal of Psychiatry*, **158**, 1680–1686.

David, S. P., Munafo, M. R., Johansen-Berg, H., Smith, S. M., Rogers, R. D., Matthews, P. M., and Walton, R. T. (2005). Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: A functional magnetic resonance imaging study. *Biological Psychiatry*, **58**, 488–494.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., and Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology*, **53**(1), 545–574.

Davis, J., Eyre, H., Jacka, F. N., Dodd, S., Dean, O., McEwen, S., McGorry, P. D., et al. (2016). A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. *Neuroscience and Biobehavioral Reviews*, **65**, 185–194.

Davis, M., Myers, K. M., Ressler, K. J., and Rothbaum, B. O. (2005). Facilitation of extinction of conditioned fear by D-cycloserine. *Current Directions in Psychological Science*, **14**, 214–219.

Dawson, G., Ashman, S. B., Hessler, D., Spieker, S., Frey, K., Panagiotides, H., and

Embry, L. (2001). Autonomic and brain electrical activity in securely- and insecurely-attached infants of depressed mothers. *Infant Behavior and Development*, **24**, 135–149.

Deldin, P. J., Keller, J., Gergen, J. A., and Miller, G. A. (2000). Right-posterior face processing anomaly in depression. *Journal of Abnormal Psychology*, **109**, 116–121.

Deveney, C. M., and Deldin, P. J. (2004). Memory of faces: A slow wave ERP study of major depression. *Emotion*, **4**, 295–304.

Diego, M. A., Field, T., Hernandez-Reif, M., Cullen, C., Schanberg, S., and Kuhn, C. (2004). Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry*, **67**, 63–80.

Disner, S. G., Beevers, C. G., Haigh, E. A., and Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, **12**, 467–477.

Dougall, N., Maayan, N., Soares-Weiser, K., McDermott, L. M., and McIntosh, A. (2015). Transcranial magnetic stimulation for schizophrenia. *Schizophrenia Bulletin*, **41**, 1220–1222.

Downar, J., and Daskalakis, Z. J. (2013). New targets for rTMS in depression: A review of convergent evidence. *Brain Stimulation*, **6**, 231–240.

Droutman, V., Read, S. J., and Bechara, A. (2015). Revisiting the role of the insula in addiction. *Trends in Cognitive Sciences*, **19**, 414–420.

Duits, P., Cath, D. C., Lissek, S., Hox, J. J., Hamm, A. O., Engelhard, I. M., Baas, J. M., et al. (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety*, **32**, 239–253.

Duman, R. S. (2004). Depression: A case of neuronal life and death? *Biological Psychiatry*, **56**, 140–145.

Duman, R. S. (2009). Neurochemical theories of depression: Preclinical studies. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (3rd edn.) (pp. 413–434). Oxford: Oxford University Press.

Dunlop, B. W., and Mayberg, H. S. (2014). Neuroimaging-based biomarkers for treatment selection in major depressive disorder. *Dialogues in Clinical Neuroscience*, **16**, 479–490.

Earls, H. A., Curran, T., and Mittal, V. (2016). A Meta-analytic review of auditory event-related potential components as endophenotypes for schizophrenia: Perspectives from first-degree relatives. *Schizophrenia Bulletin*, **42**, 1504–1516.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of COMT Val^{108/158} Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences*, **98**, 6917–6922.

Engels, A. S., Heller, W., Mohanty, A., Herrington, J. D., Banich, M. T., Webb, A. G., and Miller, G. A. (2007). Specificity of regional brain activity in anxiety types during emotion processing. *Psychophysiology*, **44**, 352–363.

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., and Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *Journal of Neuroscience*, **30**, 15726–15734.

Ersche, K. D., Barnes, A., Jones, P. S., Morein-Zamir, S., Robbins, T. W., and Bullmore, E. T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain*, **134**, 2013–2024.

Etkin, A., and Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia.

American Journal of Psychiatry, **164**, 1476–1488.

Ettinger, U., Schmechtig, A., Touloupoulou, T., Borg, C., Orrells, C., Owens, S., McGuire, P. K., et al. (2010). Prefrontal and striatal volumes in monozygotic twins concordant and discordant for schizophrenia. *Schizophrenia Bulletin*, **38**, 192–203.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., Whiteford, H. A., et al. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Medicine*, **10**, e1001547.

Filbey, F. M., Claus, E., Audette, A. R., Niculescu, M., Banich, M. T., Tanabe, J., et al. (2008). Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology*, **33**, 1391–1401.

Fisher, M., Holland, C., Merzenich, M. M., and Vinogradov, S. (2009). Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *American Journal of Psychiatry*, **166**, 805–811.

Fisher, M., Holland, C., Subramaniam, K., and Vinogradov, S. (2010). Neuroplasticity-based cognitive training in schizophrenia: An interim report on the effects 6 months later. *Schizophrenia Bulletin*, **36**, 869–879.

Ford, J. M. (1999). Schizophrenia: The broken P300 and beyond. *Psychophysiology*, **36**, 667–682.

Ford, J. M., Mathalon, D. H., Whitfield, S., Faustman, W. O., and Roth, W. T. (2002). Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biological Psychiatry*, **51**, 485–492.

Fox, M. D., Buckner, R. L., White, M. P., Greicius, M. D., and Pascual-Leone, A. (2012). Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological Psychiatry*, **72**,

595–603.

Frantseva, M., Cui, J., Farzan, F., Chinta, L. V., Velazquez, J. L. P., and Daskalakis, Z. J. (2014). Disrupted cortical conductivity in schizophrenia: TMS-EEG study. *Cerebral Cortex*, **24**, 211–221.

Friedlander, L., and Desrocher, M. (2006). Neuroimaging studies of obsessive-compulsive disorder in adults and children. *Clinical Psychology Review*, **26**, 32–49.

Fu, C. H., Steiner, H., and Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiology of Disease*, **52**, 75–83.

Furmark, T., Tillford, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B., and Fredrikson, M. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Archives of General Psychiatry*, **59**, 425–433.

Fusar-Poli, P., Howes, O. D., Allen, P., Broome, M., Valli, I., Asselin, M. C., McGuire, P., et al. (2011). Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Molecular Psychiatry*, **16**, 67–75.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J.-K., Sperry, L., Ross, T. J., et al. (2000). Cue-induced cocaine craving: Neuroanatomical specificity for drug users and drug stimuli. *American Journal of Psychiatry*, **157**, 1789–1798.

Garpenstrand, H., Annas, P., Ekblom, J., Oreland, L., and Fredrikson, M. (2001). Human fear conditioning is related to dopaminergic and serotonergic biological markers. *Behavioral Neuroscience*, **115**, 358–364.

Gehring, W. J., Himle, J., and Nisenson, L. G. (2000). Action-monitoring dysfunction in

obsessive-compulsive disorder. *Psychological Science*, **11**, 1–6.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., and Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, **5**, 1242–1247.

Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia Research*, **72**, 21–28.

Goldstein, R. Z., and Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, **12**(11), 652–669.

Gottesman, I. I. (1991). *Schizophrenia genesis: The origins of madness*. New York: W. H. Freeman.

Gratten, J., Wray, N. R., Keller, M. C., and Visscher, P. M. (2014). Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Neuroscience*, **17**(6), 782–790.

Green, M. F., Kern, R. S., and Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: Implications for MATRICS. *Schizophrenia Research*, **72**, 41–51.

Greenberg, B. D., Li, Q., Lucas, F. R., Hu, S., Sirota, L. A., Benjamin, J., et al. (2000). Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. *American Journal of Medical Genetics*, **96**, 202–216.

Grimonprez, A., Raedt, R., Baeken, C., Boon, P., and Vonck, K. (2015). The antidepressant mechanism of action of vagus nerve stimulation: Evidence from preclinical studies. *Neuroscience and Biobehavioral Reviews*, **56**, 26–34.

Groves, D. A., and Brown, V. J. (2005). Vagal nerve stimulation: A review of its applications and potential mechanisms that mediate its clinical effects. *Neuroscience and Biobehavioral Reviews*, **29**, 493–500.

Grupe, D. W., and Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*, **14**, 488–501.

Haijma, S. V., van Haren, N., Cahn, W., Koolschijn, P. C. M., Pol, H. E. H., and Kahn, R. S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin*, **39**, 1129–1138.

Hajcak, G., McDonald, N., and Simons, R. F. (2003). Anxiety and error-related brain activity. *Biological Psychology*, **64**, 77–90.

Hakamata, Y., Lissek, S., Bar-Haim, Y., Britton, J. C., Fox, N. A., Leibenluft, E., Pine, D. S., et al. (2010). Attention bias modification treatment: A meta-analysis toward the establishment of novel treatment for anxiety. *Biological Psychiatry*, **68**(11), 982–990.

Hamann, S. (2005). Blue genes: Wiring the brain for depression. *Nature Neuroscience*, **8**, 701–703.

Hamilton, J. P., Farmer, M., Fogelman, P., and Gotlib, I. H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biological Psychiatry*, **78**, 224–230.

Hamilton, J. P., and Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological Psychiatry*, **63**, 1155–1162.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, **1**, 293–319.

Hardesty, D. E., and Sackeim, H. A. (2007). Deep brain stimulation in movement and psychiatric disorders. *Biological Psychiatry*, **61**, 831–835.

Hariri, A. R., and Holmes, A. (2006). Genetics of emotional regulation: The role of the serotonin transporter in neural function. *Trends in Cognitive Sciences*, **10**, 182–191.

Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, **297**, 400–403.

Hazlett, E. A., Rothstein, E. G., Ferreira, R., Silverman, J. M., Siever, L. J., and Olincy, A. (2015). Sensory gating disturbances in the spectrum: Similarities and differences in schizotypal personality disorder and schizophrenia. *Schizophrenia Research*, **161**, 283–290.

Heinz, A., Braus, D. F., Smolka, M. N., Wraase, J., Puls, I., Hermann, D., et al. (2005). Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nature Neuroscience*, **8**, 20–21.

Heinz, A., Romero, B., Gallinat, J., Juckett, G., and Weinberger, D. R. (2003). Molecular brain imaging and the neurobiology and genetics of schizophrenia. *Pharmacopsychiatry*, **36**(Suppl. 3), 5152–5157.

Heller, W., Koven, N. S., and Miller, G. A. (2003). Regional brain activity in anxiety and depression, cognition/emotion interaction, and emotion regulation. In K. Hugdahl and R. J. Davidson (eds.), *The asymmetrical brain* (pp. 533–564). Cambridge, MA: MIT Press.

Heller, W., Nitschke, J. B., Etienne, M. A., and Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology*, **106**, 376–385.

Hill, A. S., Sahay, A., and Hen, R. (2015). Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors.

Neuropsychopharmacology, **40**, 2368–2378.

Hoefgen, B., Schulze, T. G., Ohlraun, S., von Widdern, O., Höfels, S., Gross, M., et al. (2005). The power of sample size and homogeneous sampling: Association between the 5-HTTLPR serotonin transporter polymorphism and major depressive disorder.

Biological Psychiatry, **57**, 247–251.

Holmes, A. J., and Pizzagalli, D. A. (2008). Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. Archives of General Psychiatry, **65**, 179–188.

Honea, R., Crow, T. J., Passingham, D., and Mackay, C. E. (2005). Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry studies. American Journal of Psychiatry, **162**, 2233–2245.

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., et al. (2004). Pathways that make voices: White matter changes in auditory hallucinations. Archives of General Psychiatry, **61**, 658–668.

Iosifescu, D. V., Murrough, J. W., and Charney, D. S. (2013). Treatments for depression. In D. S. Charney, P. Sklar, J. D. Buxbaum, and E. J. Nestler (eds.), Neurobiology of mental illness (4th edn.) (pp. 508–526). Oxford: Oxford University Press.

Jacobs, B. L. (2004). Depression: The brain finally gets into the act. Current Directions in Psychological Science, **13**, 103–106.

Kaiser, R. H., Andrews-Hanna, J. R., Spielberg, J. M., Warren, S. L., Sutton, B. P., Miller, G. A., Banich, M. T., et al. (2015a). Distracted and down: Neural mechanisms of affective interference in subclinical depression. Social Cognitive and Affective Neuroscience, **10**, 654–663.

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., and Pizzagalli, D. A. (2015a). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, **72**, 603–611.

Kamenov, K., Twomey, C., Cabello, M., Prina, A. M., and Ayuso-Mateos, J. L. (2017). The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: A meta-analysis. *Psychological Medicine*, **47**, 414–425.

Kandel, D. B., Hu, M.-C., and Griesler, P. C. (2013). Epidemiology of substance use disorders. In D. S. Charney, P. Sklar, J. D. Buxbaum, and E. J. Nestler (eds.), *Neurobiology of mental illness* (4th edn.) (pp. 772–787). Oxford: Oxford University Press.

Kavanagh, D. H., Tansey, K. E., O'donovan, M. C., and Owen, M. J. (2015). Schizophrenia genetics: Emerging themes for a complex disorder. *Molecular Psychiatry*, **20**, 72–76.

Kawasaki, Y., Sumiyoshi, T., Higuchi, Y., Ito, T., Takeuchi, M., and Kurachi, M. (2007). Voxel-based analysis of P300 electrophysiological topography associated with positive and negative symptoms of schizophrenia. *Schizophrenia Research*, **94**, 164–171.

Keedwell, P. A., Andrew, C., Williams, S. C. R., Brammer, M. J., and Phillips, M. L. (2005). The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, **58**, 843–853.

Kent, J. M., and Rauch, S. L. (2009). Neuroimaging studies of anxiety disorders. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (3rd edn.) (pp. 703–730). Oxford: Oxford University Press.

Kentgen, L. M., Tenke, C. E., Pine, D. S., Fong, R., Klein, R. G., and Bruder, G. E. (2000). Electroencephalographic asymmetries in adolescents with major depression:

Influence of comorbidity with anxiety disorders. *Journal of Abnormal Psychology*, **109**, 797–802.

Kerns, J. G., Cohen, J. D., MacDonald, A. W., Johnson, M. K., Stenger, V. A., Aizenstein, H., and Carter, C. S. (2005). Decreased conflict- and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. *American Journal of Psychiatry*, **162**, 1833–1839.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., and Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey replication. *Archives of General Psychiatry*, **62**, 617–627.

Kiang, M., Kutas, M., Light, G. A., and Braff, D. L. (2008). An event-related brain potential study of direct and indirect semantic priming in schizophrenia. *American Journal of Psychiatry*, **165**, 74–81.

Kirby, K. N., Petry, N. M., and Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-use controls. *Journal of Experimental Psychology: General*, **128**, 78–87.

Kito, S., Fujita, K., and Koga, Y. (2008). Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, **20**, 74–80.

Koban, L., and Pourtois, G. (2014). Brain systems underlying the affective and social monitoring of actions: An integrative review. *Neuroscience and Biobehavioral Reviews*, **46**, 71–84.

Kozak, M. J., and Cuthbert, B. N. (2016). The NIMH Research Domain Criteria initiative: Background, issues, and pragmatics. *Psychophysiology*, **53**, 286–297.

Kuperberg, G. R., Deckersbach, T., Holt, D. J., Goff, D., and West, W. C. (2007).

Increased temporal and prefrontal activity in response to semantic associations in schizophrenia. *Archives of General Psychiatry*, **64**, 138–151.

Lally, J., and MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *British Medical Bulletin*, **114**, 169–179.

Lawrie, S. M., Buechel, C., Whalley, H. C., Frith, C. D., Firston, K. J., and Johnstone, E. C. (2002). Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biological Psychiatry*, **51**, 1008–1011.

Ledgerwood, L., Richardson, R., and Cranney, J. (2003). Effects of D-cycloserine on extinction of conditioned freezing. *Behavioral Neuroscience*, **117**, 341–349.

Lee, K.-H., Williams, L. M., Breakspear, M., and Gordon, E. (2003). Synchronous gamma activity: A review and contribution to an integrative neuroscience model of schizophrenia. *Brain Research Reviews*, **41**, 57–78.

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, **274**, 1527–1531.

Lester, K. (2017). Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. *Molecular Psychiatry*, e-publication in advance of print.

Levin, R. L., Heller, W., Mohanty, A., Herrington, J. D., and Miller, G. A. (2007). Cognitive deficits in depression and functional specificity of regional brain activity. *Cognitive Therapy and Research*, **31**(2), 211–233.

Lozano, A. M., Mayberg, H. S., Giacobbe, P., Hamani, C., Craddock, R. C., and Kennedy, S. H. (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biological Psychiatry*, **64**, 461–467.

Lu, B. Y., Martin, K. E., Edgar, J. C., Smith, A. K., Lewis, S. F., Escamilla, M. A., et al. (2007). Effect of catechol-O-methyltransferase val¹⁵⁸ met polymorphism on the P50 gating endophenotype in schizophrenia. *Biological Psychiatry*, **62**, 822–825.

Lucantonio, F., Stalnaker, T. A., Shaham, Y., Niv, Y., and Schoenbaum, G. (2012). The impact of orbitofrontal dysfunction on cocaine addiction. *Nature Neuroscience*, **15**, 358–366.

Mahar, I., Bambico, F. R., Mechawar, N., and Nobrega, J. N. (2014). Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. *Neuroscience and Biobehavioral Reviews*, **38**, 173–192.

Marangell, L. B., Rush, A. J., George, M. S., Sackeim, H. A., Johnson, C. R., Husain, M. M., et al. (2002). Vagus nerve stimulation (VNS) for major depressive episodes: One year outcomes. *Biological Psychiatry*, **51**, 280–287.

Martin, J. L. R., and Martin-Sanchez, E. (2012). Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: Variable results based on study designs. *European Psychiatry*, **27**, 147–155.

Mathalon, D. H., Fedor, M., Faustman, W. O., Gray, M., Askari, N., and Ford, J. M. (2002). Response-monitoring dysfunction in schizophrenia: An event-related brain potential study. *Journal of Abnormal Psychology*, **111**, 22–41.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, Schwalb, J. M., and Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, **45**, 651–660.

McCarley, R. W., Salisbury, D. F., Hirayasu, Y., Yurgelun-Todd, D. A., Tohen, M., Zarate, C., et al. (2002). Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. *Archives of General Psychiatry*, **59**, 321–331.

McDonald, C., and Murphy, K. C. (2003). The new genetics of schizophrenia. *Psychiatric Clinics of North America*, **26**, 41–63.

McEwen, B. S. (2009). Stress-induced structural and functional plasticity in the brain: Protection, damage, and brain-body communication. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (3rd edn.) (pp. 627–654). Oxford: Oxford University Press.

McGurk, S. R., Twamley, E. W., Sitzler, D. I., McHugo, G. J., and Mueser, K. T. (2007). A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry*, **164**, 1791–1802.

Metzger, L. J., Paige, S. R., Carson, M. A., Lasko, N. B., Paulus, L. A., Pitman, R. K., and Orr, S. P. (2004). PTSD arousal and depression symptoms associated with increased right-sided parietal EEG asymmetry. *Journal of Abnormal Psychology*, **113**, 324–329.

Milad, M. R., Rauch, S. L., Pitman, R. K., and Quirk, G. J. (2006). Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biological Psychology*, **73**(1), 61–71.

Mineka, S., Rafaeli, E., and Yovel, I. (2003). Cognitive biases in emotional disorders: Information processing and social-cognitive perspectives. In R. J. Davidson, K. R. Sherer, and H. Hill Goldsmith (eds.), *Handbook of Affective Science* (pp. 976–1009). Oxford: Oxford University Press.

Minzenberg, M., Ober, B. A., and Vinogradov, S. (2002). Semantic priming in schizophrenia: A review and synthesis. *Journal of the International Neuropsychological Society*, **8**, 699–720.

Moore, H., Geyer, M. A., Carter, C. S., and Barch, D. M. (2013). Harnessing cognitive neuroscience to develop new treatments for improving cognition in schizophrenia:

CNTRICS selected cognitive paradigms for animal models. *Neuroscience and Biobehavioral Reviews*, **37**, 2087–2091.

Moser, J., Moran, T., Schroder, H., Donnellan, B., and Yeung, N. (2013). On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework. *Frontiers in Human Neuroscience*, **7**, 466.

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., and Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry*, **77**, 276–284.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., and Ustun, B. (2007). Depression, chronic disease, and decrements in health: Results from the World Health Surveys. *Lancet*, **370**, 851–858.

Mueser, K. T., and McGurk, S. R. (2004). Schizophrenia. *Lancet*, **363**, 2063–2072.

Murphy, F. C., Michael, A., Robbins, T. W., and Sahakian, B. J. (2003). Neuropsychological impairment in patients with major depressive disorder: The effects of feedback on task performance. *Psychological Medicine*, **33**, 455–467.

Murphy, S. E., Norbury, R., Godlewska, B. R., Cowen, P. J., Mannie, Z. M., Harmer, C. J., and Munafo, M. R. (2013). The effect of the serotonin transporter polymorphism (5-HTTLPR) on amygdala function: A meta-analysis. *Molecular Psychiatry*, **18**, 512–520.

Nakatani, E., Nakgawa, A., Ohara, Y., Goto, S., Uozumi, N., Iwakiri, M., et al. (2003). Effects of behavior therapy on regional cerebral blood flow in obsessive-compulsive disorder. *Psychiatry Research-Neuroimaging*, **124**, 113–120.

Naqvi, N. H., Rudrauf, D., Damasio, H., and Bechara, A. (2007). Damage to the insula disrupts addiction to cigarette smoking. *Science*, **315**, 531–534.

Nestler, E. J. (2009). Cellular and molecular mechanisms of drug addiction. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (3rd edn.) (pp. 775–785). Oxford: Oxford University Press.

Nikolova, Y. S., Koenen, K. C., Galea, S., Wang, C. M., Seney, M. L., Sibille, E., Hariri, A. R., et al. (2014). Beyond genotype: Serotonin transporter epigenetic modification predicts human brain function. *Nature Neuroscience*, **17**, 1153–1155.

Nitschke, J. B., Heller, W., and Miller, G. A. (2000). The neuropsychology of anxiety. In J. C. Borod (ed.), *The neuropsychology of emotion* (pp. 298–319). New York: Oxford University Press.

Noël, X., Brevers, D., and Bechara, A. (2013). A neurocognitive approach to understanding the neurobiology of addiction. *Current Opinion in Neurobiology*, **23**, 632–638.

Nutt, D. J., Lingford-Hughes, A., Erritzoe, D., and Stokes, P. R. (2015). The dopamine theory of addiction: 40 years of highs and lows. *Nature Reviews Neuroscience*, **16**, 305–312.

Orellana, G., and Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry*, **4**, 35.

Owens, E. M., Bachman, P., Glahn, D. C., and Bearden, C. E. (2016). Electrophysiological endophenotypes for schizophrenia. *Harvard Review of Psychiatry*, **24**, 129–147.

Palm, U., Hasan, A., Strube, W., and Padberg, F. (2016). tDCS for the treatment of depression: A comprehensive review. *European Archives of Psychiatry and Clinical Neuroscience*, **266**, 681–694.

Patrick, C. J., and Hajcak, G. (2016). RDoC: Translating promise into progress.

Psychophysiology, **53**, 415–424.

Patterson, J. V., Hetrick, W. P., Boutros, N. N., Jin, Y., Sandman, C., Stern, H., Bunney, W. E., et al. (2008). P50 sensory gating ratios in schizophrenics and controls: A review and data analysis. *Psychiatry Research*, **158**, 226–247.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., and Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biological Psychiatry*, **53**, 25–38.

Petry, N. M. (2001). Pathological gamblers, with and without substance use disorders, discount delayed rewards at high rates. *Journal of Abnormal Psychology*, **110**, 482–487.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nature Neuroscience*, **8**, 828–834.

Phillips, M. L., Chase, H. W., Sheline, Y. I., Etkin, A., Almeida, J. R., Deckersbach, T., and Trivedi, M. H. (2015). Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: Neuroimaging approaches. *American Journal of Psychiatry*, **172**(2), 124–138.

Phillips, M. L., Drevets, W. C., Rauch, S. L., and Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry*, **54**, 515–528.

Pissiota, A., Frans, O., Fernandez, M., von Knorring, L., Fischer, H., and Fredrikson, M. (2002). Neurofunctional correlates of posttraumatic stress disorder: A PET symptom provocation study. *European Archives of Psychiatry and Clinical Neurosciences*, **252**, 68–75.

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson,

M. W., Liberzon, I., et al. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*, **13**, 769–787.

Pol, H. H., and Kahn, R. (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophrenia Bulletin*, **34**, 354–366.

Preller, K. H., Herdener, M., Schilbach, L., Stämpfli, P., Hulka, L. M., Vonmoos, M., Quednow, B. B., et al. (2014). Functional changes of the reward system underlie blunted response to social gaze in cocaine users. *Proceedings of the National Academy of Sciences*, **111**, 2842–2847.

Proudfit, G. H. (2015). The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology*, **52**, 449–459.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., O'Dushlaine, C. T., et al. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, **460**, 748–752.

Rabe, S., Debener, S., Brocke, B., and Beauducel, A. (2005). Depression and its relation to posterior cortical activity during performance of neuropsychological verbal and spatial tasks. *Personality and Individual Differences*, **39**, 601–611.

Rapoport, J. L., Addington, A. M., Frangou, S., and MRC Psych. (2005). The neurodevelopmental model of schizophrenia: Update 2005. *Molecular Psychiatry*, **10**, 443–449.

Rauch, S. L., van der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, A. J., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry*, **53**, 380–387.

Reinhart, R. M., Zhu, J., Park, S., and Woodman, G. F. (2015). Medial-frontal

stimulation enhances learning in schizophrenia by restoring prediction error signaling. *Journal of Neuroscience*, **35**, 12232–12240.

Remes, O., Brayne, C., Linde, R., and Lafortune, L. (2016). A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain and Behavior*, **6**.

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T., Farh, K. H., Holmans, P. A., Pers, T. H., et al. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, **511**, 421–427.

Ritsner, M. S. (2007). Predicting quality of life impairment in chronic schizophrenia from cognitive variables. *Quality of Life Research*, **16**, 929–937.

Roiser, J. P., Elliott, R., and Sahakian, B. J. (2012). Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology*, **37**(1), 117–136.

Rush, A. J., George, M. S., Sackeim, H. A., Marangell, L. B., Husain, M. M., Giller, C., et al. (2000). Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biological Psychiatry*, **47**, 276–286.

Russo, S. J., and Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nature Reviews Neuroscience*, **14**(9), 609–626.

Safadi, Z., Lichtenstein-Vidne, L., Dobrusin, M., and Henik, A. (2013). Investigating thought disorder in schizophrenia: Evidence for pathological activation. *PloS ONE*, **8**(12), e82882.

Sahay, A., and Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nature Neuroscience*, **10**, 1110–1115.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants.

Science, **301**, 805–809.

Schacht, J. P., Anton, R. F., and Myrick, H. (2013). Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addiction Biology*, **18**, 121–133.

Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. (2011). Genome-wide association study identifies five new schizophrenia loci. *Nature Genetics*, **43**, 969–976.

Schlaepfer, T. E., Bewernick, B. H., Kayser, S., Hurlemann, R., and Coenen, V. A. (2014). Deep brain stimulation of the human reward system for major depression – rationale, outcomes and outlook. *Neuropsychopharmacology*, **39**(6), 1303.

Schnack, H. G., van Haren, N. E., Nieuwenhuis, M., Hulshoff Pol, H. E., Cahn, W., and Kahn, R. S. (2016). Accelerated brain aging in schizophrenia: A longitudinal pattern recognition study. *American Journal of Psychiatry*, **173**, 607–616.

Seidman, L. J., Thermenos, H. W., Poldrack, R. A., Peace, N. K., Koch, J. K., Faraone, S. V., and Tsuang, M. T. (2006). Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: An fMRI study of working memory. *Schizophrenia Research*, **85**, 58–72.

Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., ... and Genovese, G. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature*, **530**(7589), 177.

Shankman, S. A., Klein, D. N., Tenke, C. E., and Bruder, G. E. (2007). Reward sensitivity in depression: A biobehavioral study. *Journal of Abnormal Psychology*, **116**, 95–104.

Sharp, P. B., Miller, G. A., and Heller, W. (2015). Transdiagnostic dimensions of anxiety: Neural mechanisms, executive functions, and new directions. *International*

Journal of Psychophysiology, **98**, 365–377.

Sheffield, J. M., and Barch, D. M. (2016). Cognition and resting-state functional connectivity in schizophrenia. *Neuroscience and Biobehavioral Reviews*, **61**, 108–120.

Shenton, M. E., Dickey, C. C., Frumin, M., and McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research*, **49**, 1–52.

Sherif, M., Radhakrishnan, R., D'Souza, D. C., and Ranganathan, M. (2016). Human laboratory studies on cannabinoids and psychosis. *Biological Psychiatry*, **79**, 526–538.

Shin, L. M., Kosslyn, S. M., McNally, R. J., Alpert, N. M., Thompson, W. L., Rauch, S. L., et al. (1997). Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Archives of General Psychiatry*, **54**, 233–241.

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., and Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. *Biological Psychiatry*, **61**, 198–209.

Singh, M. K., and Gotlib, I. H. (2014). The neuroscience of depression: Implications for assessment and intervention. *Behaviour Research and Therapy*, **62**, 60–73.

Sisk, C., and Foster, D. (2004). The neural basis of puberty and adolescence. *Nature Neuroscience*, **7**, 1040–1047.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, **139**, 81–132.

Solvason, H. B., Husain, M., Fitzgerald, P. B., Rosenquist, P., McCall, W. V., Kimball, J., Lisanby, S. H., et al. (2014). Improvement in quality of life with left prefrontal transcranial magnetic stimulation in patients with pharmacoresistant major depression:

Acute and six month outcomes. *Brain Stimulation*, **7**, 219–225.

Sotres-Bayon, F., Bush, D. E. A., and LeDoux, J. E. (2004). Emotional perseveration: An update on prefrontal-amygdala interactions in fear extinction. *Learning and Memory*, **11**, 525–535.

Speer, A. M., Kimbrell, T. A., Wassermann, E. M., Repella, J. D., Willis, M. W., Herscovitch, P., and Post, R. M. (2000). Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry*, **48**, 1133–1141.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., and McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *Journal of Neuroscience*, **23**, 7407–7411.

Steele, J. D., Kumar, P., and Ebmeier, K. P. (2007). Blunted response to feedback information in depressive illness. *Brain*, **130**, 2367–2374.

Strafella, A. P., Paus, T., Barrett, J., and Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *Journal of Neuroscience*, **21**, RC157(1–4).

Tamminga, C. A., and Ivleva, E. I. (2013). Psychotic disorders: Neurochemistry and pharmacotherapy. In D. S. Charney, P. Sklar, J. D. Buxbaum, and E. J. Nestler (eds.), *Neurobiology of mental illness* (4th edn.) (pp. 346–354). Oxford: Oxford University Press.

Tanabe, J., Tregellas, J., Dalwani, M., Thompson, L., Owen, E., Crowley, T., and Banich, M. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biological Psychiatry*, **65**, 160–164.

Tanabe, J., Tregellas, J., Miller, D., Ross, R. G., and Freedman, R. (2002). Brain activation during smooth-pursuit eye movements. *NeuroImage*, **17**, 1315–1324.

Teng, S., Guo, Z., Peng, H., Xing, G., Chen, H., He, B., Mu, Q., et al. (2017). High-frequency repetitive transcranial magnetic stimulation over the left DLPFC for major depression: Session-dependent efficacy: A meta-analysis. *European Psychiatry*, **41**, 75–84.

Thibodeau, R., Jorgensen, R. S., and Kim, S. (2006). Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology*, **115**, 715–729.

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., et al. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences*, **98**, 11650–11655.

Tomarken, A. J., Dichter, G. S., Garber, J., and Simien, C. (2004). Resting frontal brain activity: Linkages to maternal depression and socio-economic status among adolescents. *Biological Psychology*, **67**, 77–102.

Tregellas, J. R., Tanabe, J. L., Miller, D. E., Ross, R. G., Olincy, A., and Freedman, R. (2004). Neurobiology of smooth pursuit eye movement deficits in schizophrenia: An fMRI study. *American Journal of Psychiatry*, **161**, 315–321.

Turetsky, B. I., Dress, E. M., Braff, D. L., Calkins, M. E., Green, M. F., Greenwood, T. A., Radant, A. D., et al. (2015). The utility of P300 as a schizophrenia endophenotype and predictive biomarker: Clinical and socio-demographic modulators in COGS-2. *Schizophrenia Research*, **163**, 53–62.

van Rooij, S. J. H., Kennis, M., Sjouwerman, R., van den Heuvel, M. P., Kahn, R. S., and Geuze, E. (2015). Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. *Psychological Medicine*, **45**, 2737–2746.

van Tol, M. J., Demenescu, L. R., van der Wee, N. J., KorteKaas, R., Marjan, N., Den

Boer, J. A., Veltman, D. J., et al. (2012). Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. *Biological Psychiatry*, **71**, 593–602.

Velligan, D., Maples, N., Roberts, D. L., and Medellin, E. M. (2014). Integrated psychosocial treatment for negative symptoms. *American Journal of Psychiatric Rehabilitation*, **17**, 1–19.

Videbech, P., and Ravnkilde, B. (2004). Hippocampal volume and depression: A meta-analysis of MRI studies. *American Journal of Psychiatry*, **161**, 1957–1966.

Vita, A., de Peri, L., Deste, G., and Sacchetti, E. (2012). Progressive loss of cortical gray matter in schizophrenia: A meta-analysis and meta-regression of longitudinal MRI studies. *Translational Psychiatry*, **2**(11), e190.

Volkow, N. D., and Morales, M. (2015). The brain on drugs: From reward to addiction. *Cell*, **162**, 712–725.

Volman, I., Verhagen, L., den Ouden, H. E., Fernández, G., Rijpkema, M., Franke, B., Roelofs, K., et al. (2013). Reduced serotonin transporter availability decreases prefrontal control of the amygdala. *Journal of Neuroscience*, **33**, 8974–8979.

Walker, D. L., Ressler, K. J., Lu, K.-T., and Davis, M. (2002). Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *Journal of Neuroscience*, **22**, 2343–2351.

Walker, E., and Bollini, A. M. (2002). Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophrenia Research*, **54**, 17–53.

Walker, E. F., Savoie, T., and Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin*, **20**, 441–451.

Walterfang, M., Wood, S. J., Velakoulis, D., and Pantelis, C. (2006). Neuropathological, neurogenetic and neuroimaging evidence for white matter pathology in schizophrenia. *Neuroscience and Biobehavioral Reviews*, **30**, 918–948.

Wang, L., Hosakere, M., Trein, J. C. L., Miller, A., Ratnanather, J. T., Barch, D. M., et al. (2007). Abnormalities of cingulate gyrus neuroanatomy in schizophrenia. *Schizophrenia Research*, **93**, 66–78.

Wessa, M., and Lois, G. (2015). Brain functional effects of psychopharmacological treatment in major depression: A focus on neural circuitry of affective processing. *Current Neuropharmacology*, **13**, 466–479.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Burstein, R., et al. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet*, **382**, 1575–1586.

Whitton, A. E., Treadway, M. T., and Pizzagalli, D. A. (2015). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*, **28**, 7–12.

Wilson, T. W., Hernandez, O. O., Asherin, R. M., Teale, P. D., Reite, M. L., and Rojas, D. C. (2008). Cortical gamma generators suggest abnormal auditory circuitry in early-onset psychosis. *Cerebral Cortex*, **18**, 371–378.

Wise, R. A., and Gardner, E. L. (2004). Animal models of addiction. In D. S. Charney and E. J. Nestler (eds.), *Neurobiology of mental illness* (2nd edn.) (pp. 683–697). Oxford: Oxford University Press.

World Health Organization. (2001). *The World Health Report 2001: Mental health: New understanding, new hope*. Geneva: Author.

Wylie, K. P., Smucny, J., Legget, K. T., and Tregellas, J. R. (2016). Targeting functional biomarkers in schizophrenia with neuroimaging. *Current Pharmaceutical Design*, **22**, 2117-2123.

Chapter 15

Adeyemi, E. I., Giedd, J. N., and Lee, N. R. (2015). A case study of brain morphometry in triplets discordant for Down syndrome. *American Journal of Medical Genetics Part A*, **167**, 1107–1110.

Aguirre, G. K., Komáromy, A. M., Cideciyan, A. V., Brainard, D. H., Aleman, T. S., Roman, A. J., et al. (2007). Canine and human visual cortex intact and responsive despite early retinal blindness from RPE65 mutation. *PLoS Medicine*, **4**, 1117–1128.

Aichberger, M. C., Busch, M. A., Reischies, F. M., Ströhle, A., Heinz, A., and Rapp, M. A. (2010). Effect of physical inactivity on cognitive performance after 2.5 years of follow-up: Longitudinal results from the Survey of Health, Ageing, and Retirement (SHARE). *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry*, **23**, 7.

Albrecht, B., Brandeis, D., Sandersleben, H. U., Valko, L., Heinrich, H., Xu, X., Asherson, P., et al. (2014). Genetics of preparation and response control in ADHD: The role of DRD4 and DAT1. *Journal of Child Psychology and Psychiatry*, **55**, 914–923.

Allen, L., Mehta, S., McClure, J. A., and Teasell, R. (2012). Therapeutic interventions for aphasia initiated more than six months post stroke: A review of the evidence. *Topics in Stroke Rehabilitation*, **19**, 523–535.

Allman, C., and Scott, R. B. (2013). Neuropsychological sequelae following pediatric stroke: A nonlinear model of age at lesion effects. *Child Neuropsychology*, **19**, 97–107.

Amedi, A., Floel, A., Knecht, S., Zohary, E., and Cohen, L. G. (2004). Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nature Neuroscience*, **7**, 1266–1270.

Amedi, A., Raz, N., Pianka, P., Malach, R., and Zohary, E. (2003). Early “visual” cortex activation correlates with superior verbal memory performance in the blind.

Nature Neuroscience, **6**, 758–766.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th edn.). Washington, DC: Author.

Anderson, V., Spencer-Smith, M., and Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, **134**, 2197–2221.

Avila, L., Riesgo, R., Pedroso, F., Goldani, M., Danesi, M., Ranzan, J., and Sleifer, P. (2010). Language and focal brain lesion in childhood. *Journal of Child Neurology*, **25**, 829–833.

Baio, J. (2012). Prevalence of autism spectrum disorders: Autism and developmental disabilities monitoring network, 14 Sites, United States, 2008. Morbidity and Mortality Weekly Report. *Surveillance Summaries*, **61**(3). Centers for Disease Control and Prevention.

Baker, J. M., Rorden, C., and Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*, **41**, 1229–1236.

Banich, M. T., Burgess, G. C., Depue, B. E., Ruzic, L., Bidwell, L. C., Hitt-Laustsen, S., et al. (2009). The neural basis of sustained and transient attentional control in young adults with ADHD. *Neuropsychologia*, **47**, 3095–3104.

Barbaro, J., and Dissanayake, C. (2009). Autism spectrum disorders in infancy and toddlerhood: A review of the evidence on early signs, early identification tools, and early diagnosis. *Journal of Developmental and Behavioral Pediatrics*, **30**(5), 447–459.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin*, **121**, 65–94.

Barnes, D. E., Yaffe, K., Satariano, W. A., and Tager, I. B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the*

American Geriatrics Society, **51**, 459–465.

Bates, E., Reilly, J., Wulfeck, B., Dronkers, N., Opie, M., Fenson, J., et al. (2001). Differential effects of unilateral lesions on language production in children and adults. *Brain and Language*, **79**, 223–265.

Bavelier, D., Dye, M. W. G., and Hauser, P. C. (2006). Do deaf individuals see better? *Trends in Cognitive Sciences*, **10**, 512–518.

Baxter, A. J., Brugha, T. S., Erskine, H. E., Scheurer, R. W., Vos, T., and Scott, J. G. (2015). The epidemiology and global burden of autism spectrum disorders. *Psychological Medicine*, **45**, 601–613.

Bedny, M., Pascual-Leone, A., Dodell-Feder, D., Fedorenko, E., and Saxe, R. (2011). Language processing in the occipital cortex of congenitally blind adults. *Proceedings of the National Academy of Sciences*, **108**, 4429–4434.

Bennett, I. J., and Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience*, **276**, 187–205.

Berardi, N., Pizzorusso, T., Ratto, G. M., and Maffei, L. (2003). Molecular basis of plasticity in the visual cortex. *Trends in Neurosciences*, **26**, 369–378.

Berger, I., Slobodin, O., and Cassuto, H. (2017). Usefulness and validity of continuous performance tests in the diagnosis of attention-deficit hyperactivity disorder children. *Archives of Clinical Neuropsychology*, **32**, 81–93.

Bergsneider, M., Hovda, D. A., McArthur, D. L., Etchepare, M., Huang, S.-C., Sehati, N., et al. (2001). Metabolic recovery following human traumatic brain injury based on FDG-PET: Time course and relationship to neurological disability. *Journal of Head Trauma Rehabilitation*, **16**, 135–148.

Bherer, L., Erickson, K. I., and Liu-Ambrose, T. (2013). A review of the effects of

physical activity and exercise on cognitive and brain functions in older adults. *Journal of Aging Research*, **2013**.

Bick, J., Zhu, T., Stamoulis, C., Fox, N. A., Zeanah, C., and Nelson, C. A. (2015). Effect of early institutionalization and foster care on long-term white matter development: A randomized clinical trial. *JAMA Pediatrics*, **169**, 211–219.

Biernaskie, J., Chernenko, G., and Corbett, D. (2004). Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *Journal of Neuroscience*, **24**, 1245–1254.

Blakemore, S. J. (2010). The developing social brain: Implications for education. *Neuron*, **65**, 744–747.

Blakemore, S.-J., den Ouden, H., Choudhury, S., and Frith, C. (2007). Adolescent development of the neural circuitry for thinking about intentions. *Social, Cognitive and Affective Neuroscience*, **2**, 130–139.

Boets, B., de Beeck, H. P. O., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., Ghesquière, P., et al. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science*, **342**, 1251–1254.

Bolton, P. F., Golding, J., Emond, A., and Steer, C. D. (2012). Autism spectrum disorder and autistic traits in the Avon Longitudinal Study of Parents and Children: Precursors and early signs. *Journal of the American Academy of Child and Adolescent Psychiatry*, **51**, 249–260.

Bourgeois, J.-P. (2001). Synaptogenesis in the neocortex of the newborn: The ultimate frontier for individuation? In C. A. Nelson and M. Luciana (eds.), *Handbook of developmental cognitive neuroscience* (pp. 23–34). Cambridge, MA: MIT Press.

Bourgeon, S., Xerri, C., and Coq, J.-O. (2004). Abilities in tactile discrimination of textures in adult rats exposed to enriched or impoverished environments. *Behavioural*

Brain Research, **153**, 217–231.

Brain Development Cooperative Group. (2012). Total and regional brain volumes in a population-based normative sample from 4 to 18 years: The NIH MRI study of normal brain development. *Cerebral Cortex*, **22**, 1–12.

Brainard, M. S., and Doupe, A. J. (2013). Translating birdsong: Songbirds as a model for basic and applied medical research. *Annual Review of Neuroscience*, **36**, 489–517.

Briones, T. L., Klintsova, A. Y., and Greenough, W. T. (2004). Stability of synaptic plasticity in the adult rat visual cortex induced by complex environment exposure. *Brain Research*, **1018**, 130–135.

Brosco, J. P., Mattingly, M., and Sanders, L. M. (2006). Impact of specific medical interventions on reducing the prevalence of mental retardation. *Archives of Pediatric and Adolescent Medicine*, **160**, 302–309.

Bruer, J. T., and Greenough, W. T. (2001). The subtle science of how experience affects the brain. In D. B. Bailey, J. T. Bruer, F. J. Symons, and J. W. Lichtman (eds.), *Critical thinking about critical periods* (pp. 209–232). Baltimore, MD: Paul H. Brookes Publishing.

Burton, H., Sinclair, R. J., and McLaren, D. G. (2004). Cortical activity to vibrotactile stimulation: An fMRI study in blind and sighted individuals. *Human Brain Mapping*, **23**, 210–228.

Burton, H., Snyder, A. Z., Conturo, T. W., Akbudak, E., Ollinger, J. M., and Raichle, M. E. (2002a). Adaptive changes in early and late blind: A fMRI study of Braille reading. *Journal of Neurophysiology*, **87**, 589–607.

Burton, H., Snyder, A. Z., Diamond, J. B., and Raichle, M. E. (2002b). Adaptive changes in early and late blind: A fMRI study of verb generation to heard nouns. *Journal of Neurophysiology*, **88**, 3359–3371.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, **17**, 85–100.

Cabeza, R., Anderson, N. D., Mangels, J. A., Nyberg, L., and Houle, S. (2000). Age-related differences in neural activity during item and temporal order memory retrieval: A positron emission tomography study. *Journal of Cognitive Neuroscience*, **12**(1), 197–206.

Cabeza, R., Daselar, S. M., Dolcos, F., Prince, S. E., Budde, M., and Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cerebral Cortex*, **14**, 364–375.

Carrion-Castillo, A., Franke, B., and Fisher, S. E. (2013). Molecular genetics of dyslexia: An overview. *Dyslexia*, **19**, 214–240.

Carstensen, L. L., Pasupathi, M., Mayr, U., and Nesselroade, J. R. (2000). Emotional experience in everyday life across the adult life span. *Journal of Personality and Social Psychology*, **79**, 644–655.

Casey, B. J., Getz, S., and Galvan, A. (2008). The adolescent brain. *Developmental Review*, **28**, 62–77.

Casey, B. J., Tottenham, N., Liston, C., and Durston, S. (2005). Imaging the developing brain: What have we learned about cognitive development? *Trends in Cognitive Sciences*, **9**, 104–110.

Choudhury, S., Blakemore, S.-J., and Charman, T. (2006). Social cognitive development during adolescence. *Social, Cognitive and Affective Neuroscience*, **1**, 165–174.

Copeland, B. J., and Pillsbury III, H. C. (2004). Cochlear implantation for the treatment of deafness. *Annual Review of Medicine*, **55**, 157–167.

Corbetta, M. (2012). Functional connectivity and neurological recovery. *Developmental*

Psychobiology, **54**, 239–253.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., and Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*, **169**(10), 1038–1055.

Costanzo, V., Chericoni, N., Amendola, F. A., Casula, L., Muratori, F., Scattoni, M. L., and Apicella, F. (2015). Early detection of autism spectrum disorders: From retrospective home video studies to prospective “high risk” sibling studies. *Neuroscience and Biobehavioral Reviews*, **55**, 627–635.

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of Neurology*, **63**, 272–287.

Cramer, S. C., and Crafton, K. R. (2006). Somatotopy and movement representation sites following cortical stroke. *Experimental Brain Research*, **168**, 25–32.

Curtiss, S. (1977). *Genie: A psycholinguistic study of a modern-day “wild child.”* New York: Academic Press.

Daley, D., van der Oord, S., Ferrin, M., Danckaerts, M., Doepfner, M., Cortese, S., et al. and European ADHD Guidelines Group. (2014). Behavioral interventions in attention-deficit/hyperactivity disorder: A meta-analysis of randomized controlled trials across multiple outcome domains. *Journal of the American Academy of Child and Adolescent Psychiatry*, **53**, 835–847.

Dancause, N., Barbay, S., Frost, S. B., Plautz, E. J., Chen, D., Zoubina, E. V., et al. (2005). Extensive cortical rewiring after brain injury. *Journal of Neuroscience*, **25**, 10167–10179.

Davey, C. G., Yücel, M., and Allen, N. B. (2008). The emergence of depression in adolescence: Development of the prefrontal cortex and the representation of reward. *Neuroscience and Biobehavioral Reviews*, **32**, 1–19.

de Aguiar, V., Paolazzi, C. L., and Miceli, G. (2015). tDCS in post-stroke aphasia: The role of stimulation parameters, behavioral treatment and patient characteristics. *Cortex*, **63**, 296–316.

Dennis, E. L., Jahanshad, N., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Hickie, I. B., Thompson, P. M., et al. (2013). Development of brain structural connectivity between ages 12 and 30: A 4-Tesla diffusion imaging study in 439 adolescents and adults. *Neuroimage*, **64**, 671–684.

Dennis, M. (2010). Margaret Kennard (1899–1975): Not a “principle” of brain plasticity but a founding mother of developmental neuropsychology. *Cortex*, **46**, 1043–1059.

Depue, B. E., Burgess, G. C., Willcutt, E. G., Bidwell, L. C., Ruzic, L., and Banich, M. T. (2010a). Symptom-correlated brain regions in young adults with combined-type ADHD: Their organization, variability, and relation to behavioral performance. *Psychiatry Research*, **182**, 96–102.

Depue, B. E., Burgess, G. C., Willcutt, E. G., Ruzic, L., and Banich, M. T. (2010b). Inhibitory control of memory retrieval and motor processing associated with the right lateral prefrontal cortex: Evidence from deficits in individuals with ADHD. *Neuropsychologia*, **48**, 3909–3917.

De Rubeis, S., He, X., Goldberg, A. P., Poultney, C. S., Samocha, K., Cicek, A. E., Singh, T., et al. (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*, **515**, 209–215.

DeStefano, F., Price, C. S., and Weintraub, E. S. (2013). Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *The Journal of Pediatrics*, **163**, 561–567.

Dhanushkodi, A., Bindu, B., Raju, T. R., and Kutty, B. M. (2007). Exposure to enriched

environment improves spatial learning performances and enhances cell density but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats. *Behavioral Neuroscience*, **121**, 491–500.

Diamond, A., and Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science*, **333**, 959–964.

DiCicco-Bloom, E., Lord, C., Zwaigenbaum, L., Courchesne, E., Dager, S. R., Schmitz, C., et al. (2006). The developmental neurobiology of autism spectrum disorder. *Journal of Neuroscience*, **26**, 6897–6906.

Dimyan, M. A., and Cohen, L. G. (2011). Neuroplasticity in the context of motor rehabilitation after stroke. *Nature Reviews Neurology*, **7**, 76–85.

Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., ... and Barnes, K. A. (2010). Prediction of individual brain maturity using fMRI. *Science*, **329**(5997), 1358–1361.

Douaud, G., Groves, A. R., Tamnes, C. K., Westlye, L. T., Duff, E. P., Engvig, A., Matthews, P. M., et al. (2014). A common brain network links development, aging, and vulnerability to disease. *Proceedings of the National Academy of Sciences*, **111**, 17648–17653.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., and May, A. (2004). Changes in gray matter induced by training. *Nature*, **427**, 311–312.

Duval, J., Braun, C. M., Montour-Proulx, I., Daigneault, S., Rouleau, I., and Bégin, J. (2008). Brain lesions and IQ: Recovery versus decline depends on age of onset. *Journal of Child Neurology*, **23**, 663–668.

Dye, M. W., and Bavelier, D. (2010). Attentional enhancements and deficits in deaf populations: An integrative review. *Restorative Neurology and Neuroscience*, **28**, 181–192.

Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín, C., Yasamy, M. T., et al. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism Research*, **5**, 160–179.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Wojcicki, T. R., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, **108**, 3017–3022.

Farah, M. J., Shera, D. M., Savage, J. H., Betancourt, L., Giannetta, J. M., Brodsky, N. L., et al. (2006). Childhood poverty: Specific associations with neurocognitive development. *Brain Research*, **1110**, 166–174.

Feldman, H. M., and Reiff, M. I. (2014). Attention deficit–hyperactivity disorder in children and adolescents. *New England Journal of Medicine*, **370**, 838–846.

Fine, I., Wade, I. R., Brewer, A. A., May, M. G., Goodman, D. F., Boynton, G. M., et al. (2003). Long-term deprivation affects visual perception and cortex. *Nature Neuroscience*, **6**, 915–916.

Finn, E. S., Shen, X., Holahan, J. M., Scheinost, D., Lacadie, C., Papademetris, X., Constable, R. T., et al. (2014). Disruption of functional networks in dyslexia: A whole-brain, data-driven analysis of connectivity. *Biological Psychiatry*, **76**, 397–404.

Flor, H., Nikolajsen, L., and Jensen, T. S. (2006). Phantom limb pain: A case of maladaptive CNS plasticity? *Nature Reviews Neuroscience*, **7**, 873–881.

Forrest, B. J. (2004). The utility of math difficulties, internalized psychopathology, and visual-spatial deficits to identify children with the nonverbal learning disability syndrome: Evidence for a visual-spatial disability. *Child Neuropsychology*, **10**, 129–146.

Fox, N. A., et al. (2011). The effects of severe psychosocial deprivation and foster care

intervention on cognitive development at 8 years of age: Findings from the Bucharest Early Intervention Project. *Journal of Child Psychology and Psychiatry*, **52**, 919–928.

Franke, B., Faraone, S. V., Asherson, P., Buitelaar, J., Bau, C. H. D., Ramos-Quiroga, J. A., Lesch, K. P., et al. (2012). The genetics of attention deficit/hyperactivity disorder in adults, a review. *Molecular Psychiatry*, **17**, 960–987.

Friedmann, N., and Rusou, D. (2015). Critical period for first language: The crucial role of language input during the first year of life. *Current Opinion in Neurobiology*, **35**, 27–34.

Friske, J. E., and Gammie, S. C. (2005). Environmental enrichment alters plus maze, but not maternal defense performance in mice. *Physiology and Behavior*, **85**, 187–194.

Frost, S. B., Barbay, S., Friel, K. M., Plautz, E. J., and Nudo, R. J. (2003). Reorganization of remote cortical regions after ischemic brain injury: A potential substrate for stroke recovery. *Journal of Neurophysiology*, **89**, 3205–3214.

Gadad, B. S., Li, W., Yazdani, U., Grady, S., Johnson, T., Hammond, J., Ferrier, C., et al. (2015). Administration of thimerosal-containing vaccines to infant rhesus macaques does not result in autism-like behavior or neuropathology. *Proceedings of the National Academy of Sciences*, **112**, 12498–12503.

Galaburda, A. M., LoTurco, J., Ramus, F., Fitch, R. H., and Rosen, G. D. (2006). From genes to behavior in developmental dyslexia. *Nature Neuroscience*, **9**, 1213–1217.

Geranmayeh, F., Brownsett, S. L., and Wise, R. J. (2014). Task-induced brain activity in aphasic stroke patients: What is driving recovery? *Brain*, **137**, 2632–2648.

Gernsbacher, M. A., Dawson, M., and Goldsmith, H. H. (2005). Three reasons not to believe in an autism epidemic. *Current Directions in Psychological Science*, **14**, 55–58.

Giedd, J. N., Raznahan, A., Alexander-Bloch, A., Schmitt, E., Gogtay, N., and

Rapoport, J. L. (2015). Child psychiatry branch of the National Institute of Mental Health longitudinal structural magnetic resonance imaging study of human brain development. *Neuropsychopharmacology*, **40**, 43–49.

Gleitman, L., and Newport, E. (2002). The invention of language by children: Environmental and biological influences. In D. J. Levitin (ed.), *Foundations of cognitive psychology: Core readings* (pp. 685–704). Cambridge, MA: MIT Press.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, **101**, 8174–8179.

Goswami, U. (2011). A temporal sampling framework for developmental dyslexia. *Trends in Cognitive Sciences*, **15**, 3–10.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, **13**, 491–505.

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences*, **1124**, 127–144.

Grayson, D. S., and Fair, D. A. (2017). Development of large-scale functional networks from birth to adulthood: A guide to neuroimaging literature. *NeuroImage*, **160**, 15–31.

Grefkes, C., and Fink, G. R. (2014). Connectivity-based approaches in stroke and recovery of function. *The Lancet Neurology*, **13**, 206–216.

Grossman, A. W., Aldridge, G. M., Weiler, I. J., and Greenough, W. T. (2006). Local protein synthesis and spine morphogenesis: Fragile X syndrome and beyond. *Journal of Neuroscience*, **26**, 7151–7155.

Hamilton, R. H., Chrysikou, E. G., and Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain and Language*,

118, 40–50.

Hänggi, J., Langer, N., Lutz, K., Birrer, K., Mérillat, S., and Jäncke, L. (2015). Structural brain correlates associated with professional handball playing. *PloS ONE*, **10**, e0124222.

Harlow, H. F., Dodsworth, R. O., and Harlow, M. K. (1965). Total social isolation in monkeys. *Proceedings of the National Academy of Sciences*, **54**, 90–97.

He, C. X., and Portera-Cailliau, C. (2013). The trouble with spines in fragile X syndrome: Density, maturity and plasticity. *Neuroscience*, **251**, 120–128.

Heal, D. J., Smith, S. L., and Findling, R. L. (2012). ADHD: Current and future therapeutics. *Current Topics in Behavioral Neurosciences*, **9**, 361–390.

Hedden, T., and Gabrieli, J. D. E. (2004). Insights into the aging mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience*, **5**, 87–97.

Hertzog, C., Kramer, A. F., Wilson, R. S., and Lindenberger, U. (2009). Enrichment effects on adult cognitive development: Can the functional capacity of older adults be preserved and enhanced? *Psychological Science in the Public Interest*, **9**, 1–65.

Hillman, C. H., Erickson, K. I., and Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews Neuroscience*, **9**, 58–65.

Höller-Wallscheid, M. S., Thier, P., Pomper, J. K., and Lindner, A. (2017). Bilateral recruitment of prefrontal cortex in working memory is associated with task demand but not with age. *Proceedings of the National Academy of Sciences*, **114**, E830–E839.

Horton, J. C., and Hocking, D. R. (1997). Timing of the critical period for plasticity of ocular dominance columns in the macaque striate cortex. *Journal of Neuroscience*, **17**, 3684–3709.

Huang, B. H. (2014). The effects of age on second language grammar and speech production. *Journal of Psycholinguistic Research*, **43**, 397–420.

Huang, J., Zhu, T., Qu, Y., and Mu, D. (2016). Prenatal, perinatal and neonatal risk factors for intellectual disability: A systemic review and meta-analysis. *PloS ONE*, **11**(4), e0153655.

Huang-Pollock, C. L., Karalunas, S. L., Tam, H., and Moore, A. N. (2012). Evaluating vigilance deficits in ADHD: A meta-analysis of CPT performance. *Journal of Abnormal Psychology*, **121**, 360–371.

Huddleston, L. B., Visootsak, J., and Sherman, S. L. (2014). Cognitive aspects of fragile X syndrome. *Wiley Interdisciplinary Reviews: Cognitive Science*, **5**, 501–508.

Hunter, J., Rivero-Arias, O., Angelov, A., Kim, E., Fotheringham, I., and Leal, J. (2014). Epidemiology of fragile X syndrome: A systematic review and meta-analysis. *American Journal of Medical Genetics Part A*, **164**, 1648–1658.

Huttenlocher, P. R. (1979). Synaptic density in human frontal cortex: Developmental changes and effects of aging. *Brain Research*, **163**, 195–205.

Huttenlocher, P. R. (2002). *Neural plasticity: The effects of environment on the development of the cerebral cortex*. Cambridge, MA: Harvard University Press.

Huttenlocher, P. R., and de Courten, C. (1987). The development of synapses in striate cortex of man. *Human Neurobiology*, **6**, 1–9.

Hviid, A., Stellfeld, M., Wohlfahrt, J., and Melbye, M. (2003). Association between thimerosal-containing vaccine and autism. *JAMA*, **290**, 1763–1766.

Hyde, J. S., Mezulis, A. H., and Abramson, L. Y. (2008). The ABCs of depression: Integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. *Psychological Review*, **115**, 291–313.

Jain, A., Marshall, J., Buikema, A., Bancroft, T., Kelly, J. P., and Newschaffer, C. J. (2015). Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA*, **313**, 1534–1540.

Janssen, H., Ada, L., Bernhardt, J., McElduff, P., Pollack, M., Nilsson, M., and Spratt, N. J. (2014). An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: A pilot non-randomized controlled trial. *Disability and Rehabilitation*, **36**, 255–262.

Jiang, H. Y., Xu, L. L., Shao, L., Xia, R. M., Yu, Z. H., Ling, Z. X., Ruan, B., et al. (2016). Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, e-publication in advance of print.

Johnson, E. M. (2013). Environmental enrichment protects against functional deficits caused by traumatic brain injury. *Frontiers in Behavioral Neuroscience*, **7**, 44.

Johnson, J. S., and Newport, E. L. (1989). Critical period effects in second language learning: The influence of maturational state on the acquisition of English as a second language. *Cognitive Psychology*, **21**(1), 60–99.

Jones, T. A., and Schallert, T. (1994). Use-dependent growth of pyramidal neurons after cortical damage. *Journal of Neuroscience*, **14**, 2140–2152.

Kaas, J. (2000). The reorganization of sensory and motor maps after injury in adult mammals. In M. S. Gazzaniga (ed.), *The new cognitive neurosciences* (pp. 223–236). Cambridge, MA: MIT Press.

Kalia, A., Lesmes, L. A., Dorr, M., Gandhi, T., Chatterjee, G., Ganesh, S., Sinha, P., et al. (2014). Development of pattern vision following early and extended blindness. *Proceedings of the National Academy of Sciences*, **111**, 2035–2039.

Karatekin, C. (2001). Developmental disorders of attention. In C. A. Nelson and M. Luciana (eds.), *Handbook of developmental cognitive neuroscience* (pp. 561–576). Cambridge, MA: MIT Press.

Karns, C. M., Dow, M. W., and Neville, H. J. (2012). Altered cross-modal processing in the primary auditory cortex of congenitally deaf adults: A visual-somatosensory fMRI study with a double-flash illusion. *Journal of Neuroscience*, **32**, 9626–9638.

Karr, J. E., Areshenkoff, C. N., Rast, P., and Garcia-Barrera, M. A. (2014). An empirical comparison of the therapeutic benefits of physical exercise and cognitive training on the executive functions of older adults: A meta-analysis of controlled trials. *Neuropsychology*, **28**, 829–845.

Kaufmann, W. E., and Moser, H. W. (2000). Dendritic anomalies in disorders associated with mental retardation. *Cerebral Cortex*, **10**, 981–991.

Kelly, A. C., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., Milham, M. P., et al. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex*, **19**, 640–657.

Kempermann, G., Gast, D., and Gage, F. H. (2002). Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Annals of Neurology*, **52**, 135–143.

Kennard, M. A. (1936). Age and other factors in motor recovery from precentral lesions in monkeys. *Journal of Neurophysiology*, **1**, 477–496.

Kennard, M. A. (1942). Cortical reorganization of motor function. *Archives of Neurological Psychiatry*, **48**, 227–240.

Kéri, S., and Benedek, G. (2011). Fragile X protein expression is linked to visual functions in healthy male volunteers. *Neuroscience*, **192**, 345–350.

Klinke, R., Kral, A., Heid, S., Tillien, J., and Hartmann, R. (1999). Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science*, **285**, 1729–1733.

Kodituwakku, P., and Kodituwakku, E. (2014). Cognitive and behavioral profiles of children with fetal alcohol spectrum disorders. *Current Developmental Disorders Reports*, **1**, 149–160.

Kolb, B., and Gibb, R. (2001). Early brain injury, plasticity, and behavior. In C. A. Nelson and M. Luciana (eds.), *Handbook of developmental cognitive neuroscience* (pp. 175–190). Cambridge, MA: MIT Press.

Koukoui, S. D., and Chaudhuri, A. (2007). Neuroanatomical, molecular genetic, and behavioral correlates of fragile X syndrome. *Brain Research Reviews*, **53**, 27–38.

Krakowiak, P., Walker, C. K., Bremer, A. A., Baker, A. S., Ozonoff, S., Hansen, R. L., and Hertz-Picciotto, I. (2012). Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics*, **129**, e1121–e1128.

Kral, A., and O'Donoghue, G. M. (2010). Profound deafness in childhood. *New England Journal of Medicine*, **363**, 1438–1450.

Kramer, A. F., and Erickson, K. I. (2007). Capitalizing on cortical plasticity: Influence of physical activity on cognition and brain function. *Trends in Cognitive Sciences*, **11**, 342–348.

Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., et al. (1999). Aging, fitness and neurocognitive function. *Nature*, **400**(6743), 418–419.

Kuhl, P. K. (2010). Brain mechanisms in early language acquisition. *Neuron*, **67**, 713–727.

Kupers, R., and Ptito, M. (2014). Compensatory plasticity and cross-modal

reorganization following early visual deprivation. *Neuroscience and Biobehavioral Reviews*, **41**, 36–52.

LaMantia, A. S., and Rakic, P. (1990). Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. *Journal of Neuroscience*, **10**, 2156–2175.

Land, R., Baumhoff, P., Tillein, J., Lomber, S. G., Hubka, P., and Kral, A. (2016). Cross-modal plasticity in higher-order auditory cortex of congenitally deaf cats does not limit auditory responsiveness to cochlear implants. *Journal of Neuroscience*, **36**, 6175–6185.

Lee, N. R., Adeyemi, E. I., Lin, A., Clasen, L. S., Lalonde, F. M., Condon, E., Giedd, J. N., et al. (2016). Dissociations in cortical morphometry in youth with Down syndrome: Evidence for reduced surface area but increased thickness. *Cerebral Cortex*, **26**, 2982–2990.

Leggio, M. G., Madolesi, L., Federico, F., Spirito, F., Ricci, B., Gelfo, F., and Petrosini, L. (2005). Environmental enrichment promotes improved spatial abilities and enhanced dendritic growth in the rat. *Behavioural Brain Research*, **163**, 78–90.

Lehongre, K., Ramus, F., Villiermet, N., Schwartz, D., and Giraud, A. L. (2011). Altered low-gamma sampling in auditory cortex accounts for the three main facets of dyslexia. *Neuron*, **72**, 1080–1090.

Lemere, C. A., Blusztajn, J. K., Yamaguchi, H., Wisniewski, T., Saido, T. C., and Selkoe, D. J. (1996). Sequence of deposition of heterogeneous amyloid β -peptides and APO E in Down syndrome: Implications for initial events in amyloid plaque formation. *Neurobiology of Disease*, **3**, 16–32.

Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., Thompson, P. M., et al. (2007). Sexual dimorphism of brain developmental

trajectories during childhood and adolescence. *Neuroimage*, **36**, 1065–1073.

Levin, N., Dumoulin, S. O., Winawer, J., Dougherty, R. F., and Wandell, B. A. (2010). Cortical maps and white matter tracts following long period of visual deprivation and retinal image restoration. *Neuron*, **65**, 21–31.

Levine, S. C., Kraus, R., Alexander, E., Suriyakham, L. W., and Huttenlocher, P. (2005). IQ decline following early unilateral brain injury: A longitudinal study. *Brain and Cognition*, **59**, 114–123.

Li, S.-C., and Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In L.-G. Nilsson and H. J. Markowitsch (eds.), *Cognitive neuroscience of memory* (pp. 103–146). Seattle, WA: Hogrefe and Huber.

Lindenberger, U. (2014). Human cognitive aging: Corriger la fortune? *Science*, **346**, 572–578.

Logan, G. D., Cowan, W. B., and Davis, K. A. (1984). On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance*, **10**, 276–291.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., and Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. *Neuron*, **33**, 827–840.

Lomber, S. G., Meredith, M. A., and Kral, A. (2010). Cross-modal plasticity in specific auditory cortices underlies visual compensations in the deaf. *Nature Neuroscience*, **13**, 1421–1427.

Low, L. K., and Cheng, H.-J. (2006). Axon pruning: An essential step underlying the developmental plasticity of neuronal connections. *Philosophical Transactions of the*

Royal Society B, **361**, 1531–1544.

Luciana, M. (2013). Adolescent brain development in normality and psychopathology. *Development and Psychopathology*, **25**, 1325–1345.

Lyall, K., Schmidt, R. J., and Hertz-Picciotto, I. (2014). Maternal lifestyle and environmental risk factors for autism spectrum disorders. *International Journal of Epidemiology*, **43**, 443–464.

Madsen, K. M., Lauritsen, M. B., Pedersen, C. B., Thorsen, P., Plesner, A.-M., Andersen, P. H., and Mortensen, P. B. (2003). Thimerosal and the occurrence of autism: Negative ecological evidence from Danish population-based data. *Pediatrics*, **112**, 604–606.

Makin, T. R., Scholz, J., Slater, D. H., Johansen-Berg, H., and Tracey, I. (2015). Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain*, **138**, 2140–2146.

Makinodan, M., Rosen, K. M., Ito, S., and Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science*, **337**, 1357–1360.

Marcotte, K., Perlberg, V., Marrelec, G., Benali, H., and Ansaldo, A. I. (2013). Default-mode network functional connectivity in aphasia: Therapy-induced neuroplasticity. *Brain and Language*, **124**, 45–55.

Martin, A., Kronbichler, M., and Richlan, F. (2016). Dyslexic brain activation abnormalities in deep and shallow orthographies: A meta-analysis of 28 functional neuroimaging studies. *Human Brain Mapping*, **37**, 2676–2699.

Mather, M. (2012). The emotion paradox in the aging brain. *Annals of the New York Academy of Sciences*, **1251**(1), 33–49.

Mather, M., Canli, T., English, T., Whitfield, S., Waid, P., Ochsner, K., et al. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science*, **15**, 259–267.

Matthews, P. M., and Hampshire, A. (2016). Clinical concepts emerging from fMRI functional connectomics. *Neuron*, **91**, 511–528.

Maurer, D., and Lewis, T. L. (2013). Sensitive periods in visual development. In P. D. Zelazo (ed.), *The Oxford handbook of developmental psychology*, Vol. I. New York: Oxford University Press.

May, P. A., Baete, A., Russo, J., Elliott, A. J., Blankenship, J., Kalberg, W. O., Adam, M. P., et al. (2014). Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics*, **134**, 855–866.

May, P. A., Gossage, J. P., Kalberg, W. O., Robinson, L. K., Buckley, D., Manning, M., and Hoyme, H. E. (2009). Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Developmental Disabilities Research Reviews*, **15**, 176–192.

Mazumdar, S., Winter, A., Liu, K. Y., and Bearman, P. (2013). Spatial clusters of autism births and diagnoses point to contextual drivers of increased prevalence. *Social Science and Medicine*, **95**, 87–96.

McAuley, T., Crosbie, J., Charach, A., and Schachar, R. (2014). The persistence of cognitive deficits in remitted and unremitted ADHD: A case for the state-independence of response inhibition. *Journal of Child Psychology and Psychiatry*, **55**, 292–300.

McCarthy, H., Skokauskas, N., and Frodl, T. (2014). Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: A meta-analysis. *Psychological Medicine*, **44**, 869–880.

Memo, L., Gnoato, E., Caminiti, S., Pichini, S., and Tarani, L. (2013). Fetal alcohol spectrum disorders and fetal alcohol syndrome: The state of the art and new diagnostic tools. *Early Human Development*, **89**, S40–S43.

Middeldorp, C. M., Hammerschlag, A. R., Ouwens, K. G., Groen-Blokhuis, M. M., Pourcain, B. S., Greven, C. U., Vilor-Tejedor, N., et al. (2016). A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. *Journal of the American Academy of Child and Adolescent Psychiatry*, **55**, 896–905.

Mikels, J. A., Larkin, G. R., Reuter-Lorenz, P. A., and Carstensen, L. L. (2005). Divergent trajectories in the aging mind: Changes in working memory for affective versus visual information with age. *Psychology and Aging*, **20**, 542–553.

Mooney, R. (2009). Neural mechanisms for learned birdsong. *Learning and Memory*, **16**, 655–669.

Moore, D. R., and Shannon, R. V. (2009). Beyond cochlear implants: Awakening the deafened brain. *Nature Neuroscience*, **12**, 686–691.

MTA Cooperative Group. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, **56**, 1073–1086.

Munoz-Cespedes, J. M., Rios-Lago, M., Paul, N., and Maestu, F. (2005). Functional neuroimaging studies of cognitive recovery after acquired brain damage in adults. *Neuropsychology Review*, **15**, 169–183.

Murphy, T. H., and Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. *Nature Reviews Neuroscience*, **10**, 861–872.

Myers, C. A., Vandermosten, M., Farris, E. A., Hancock, R., Gimenez, P., et al. (2014).

White matter morphometric changes uniquely predict children's reading acquisition. *Psychological Science*, **25**, 1870–1883.

Nelson, C. A., Fox, N. A., and Zeanah, C. H. (2013). Anguish of the abandoned child. *Scientific American*, **308**(4), 62–67.

Nelson, C., Fox, N., and Zeanah, C. (2014). Romania's abandoned children: Deprivation, brain development, and the struggle for recovery. Cambridge, MA: Harvard University Press.

Nelson, C. A., Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., and Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science*, **318**, 1937–1940.

Newport, E. L., Bavelier, D., and Neville, H. J. (2001). Critical thinking about critical periods: Perspectives on a critical period for language acquisition. In E. Dupoux (ed.), *Language, brain, and cognitive development* (pp. 481–502). Cambridge, MA: MIT Press.

Noble, K. G. (2014). Rich man, poor man: Socioeconomic adversity and brain development. In *Cerebrum: the Dana forum on brain science* (Vol. **2014**). New York: Dana Foundation.

Norman, L. J., Carlisi, C., Lukito, S., Hart, H., Mataix-Cols, D., Radua, J., and Rubia, K. (2016). Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: A comparative meta-analysis. *JAMA Psychiatry*, **73**, 815–825.

Nudo, R. J. (2006). Mechanisms for recovery of motor function following cortical damage. *Current Opinion in Neurobiology*, **16**, 638–644.

Nudo, R. J. (2013). Recovery after brain injury: Mechanisms and principles. *Frontiers in Human Neuroscience*, **7**.

O'Keeffe, F., Liégeois, F., Eve, M., Ganesan, V., King, J., and Murphy, T. (2014). Neuropsychological and neurobehavioral outcome following childhood arterial ischemic stroke: Attention deficits, emotional dysregulation, and executive dysfunction. *Child Neuropsychology*, **20**, 557–582.

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., and Smith, M. R. (2004). Aging reduced neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences*, **101**, 13091–13095.

Park, D. C., and Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, **60**, 173–196.

Park, J., Carp, J., Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Huang, C. M., Park, D. C., et al. (2012). Neural broadening or neural attenuation? Investigating age-related dedifferentiation in the face network in a large lifespan sample. *Journal of Neuroscience*, **32**, 2154–2158.

Parker, S. W., and Nelson, C. A. (2005). The impact of early institutional rearing on the ability to discriminate facial expressions of emotion: An event-related potential study. *Child Development*, **76**, 54–72.

Parker, S. W., Nelson, C. A., and Bucharest Early Intervention Project Core Group. (2007). Erratum: An event-related potential study of the impact of institutional rearing on face recognition. *Development and Psychopathology*, **19**, 623–625.

Patterson, T., Rapsey, C. M., and Glue, P. (2013). Systematic review of cognitive development across childhood in Down syndrome: Implications for treatment interventions. *Journal of Intellectual Disability Research*, **57**, 306–318.

Paulesu, E., Demonet, J.-F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., et al. (2001). Dyslexia: Cultural diversity and biological unity. *Science*, **291**, 2165–2167.

Pelham Jr., W. E., and Fabiano, G. A. (2008). Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child and Adolescent Psychology*, **37**, 184–214.

Petanjek, Z., Judaš, M., Šimić, G., Rašin, M. R., Uylings, H. B., Rakic, P., and Kostović, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences*, **108**, 13281–13286.

Peterson, R. L., and Pennington, B. F. (2012). Developmental dyslexia. *The Lancet*, **379**, 1997–2007.

Peterson, R. L., and Pennington, B. F. (2015). Developmental dyslexia. *Annual Review of Clinical Psychology*, **11**, 283–307.

Pfeiffer, B. E., and Huber, K. M. (2009). The state of synapses in Fragile X syndrome. *Neuroscientist*, **15**, 549–567.

Plichta, M. M., and Scheres, A. (2014). Ventral–striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: A meta-analytic review of the fMRI literature. *Neuroscience and Biobehavioral Reviews*, **38**, 125–134.

Plichta, M. M., and Scheres, A. (2015). Measuring the neural basis of reward anticipation and reward receipt in attention-deficit/hyperactivity disorder: The importance of task design. *Journal of the American Academy of Child and Adolescent Psychiatry*, **54**, 685–686.

Pliszka, S. R., et al. (2006). Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naïve or in long-term treatment. *American Journal of Psychiatry*, **163**, 1052–1060.

Proksch, J., and Bavelier, D. (2002). Changes in the spatial distribution of visual

attention after early deafness. *Journal of Cognitive Neuroscience*, **14**, 687–701.

Rakic, P. (1991). Plasticity of cortical development. In S. E. Brauth, W. S. Hall, and R. J. Dooling (eds.), *Plasticity of development* (pp. 127–161). Cambridge, MA: MIT Press.

Ramachandran, V. S., and Hirstein, W. (1998). The perception of phantom limbs. *Brain*, **121**, 1603–1630.

Rangmar, J., Hjern, A., Vinnerljung, B., Strömland, K., Aronson, M., and Fahlke, C. (2015). Psychosocial outcomes of fetal alcohol syndrome in adulthood. *Pediatrics*, **135**, e52–e58.

Raschle, N. M., Chang, M., and Gaab, N. (2011). Structural brain alterations associated with dyslexia predate reading onset. *Neuroimage*, **57**, 742–749.

Raz, N. (2001). Ageing and the brain. *eLS*.

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., and Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. *Neuroimage*, **51**, 501–511.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., et al. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, **15**, 1676–1689.

Reed, A. E., and Carstensen, L. L. (2012). The theory behind the age-related positivity effect. *Frontiers in Psychology*, **3**(339), 1–9.

Reuter-Lorenz, P. A., Marshuetz, C., Jones, J., Smith, E. E., Hartley, A., and Koeppel, R. (2001). Neurocognitive ageing of storage and executive processes. *European Journal of Cognitive Psychology*, **13**, 257–278.

Reuter-Lorenz, P. A., and Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review*, **24**, 355–370.

Richlan, F., Kronbichler, M., and Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: A quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping*, **30**, 3299–3308.

Röder, B., Stock, O., Bien, S., Neville, H., and Rösler, F. (2002). Speech processing activates visual cortex in congenitally blind humans. *European Journal of Neuroscience*, **16**, 930–936.

Ropers, H. H. (2008). Genetics of intellectual disability. *Current Opinion in Genetics and Development*, **18**, 241–250.

Rosen, A. C., Prull, M. W., O'Hara, R., Race, E., Desmond, J. E., Glover, G. H., et al. (2002). Variable effects of aging on frontal lobe contributions to memory. *NeuroReport*, **13**, 2425–2428.

Rosenberg, M. D., Finn, E. S., Scheinost, D., Papademetris, X., Shen, X., Constable, R. T., and Chun, M. M. (2016a). A neuromarker of sustained attention from whole-brain functional connectivity. *Nature Neuroscience*, **19**, 165–171.

Rosenberg, M. D., Zhang, S., Hsu, W.-T., Scheinost, D., Finn, E. S., Shen, X., et al. (2016b). Methylphenidate modulates functional network connectivity to enhance attention. *Journal of Neuroscience*, **36**, 9547–9557.

Rosenzweig, M. R., Bennett, E. L., and Diamond, M. C. (1972). Brain changes in response to experience. *Scientific American*, **226**, 22–29.

Roussotte, F., Soderberg, L., and Sowell, E. (2010). Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: Evidence from neuroimaging. *Neuropsychology Review*, **20**, 376–397.

Rubia, K. (2011). “Cool” inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus “hot” ventromedial orbitofrontal-limbic dysfunction in conduct disorder: A review. *Biological Psychiatry*, **69**, e69–87.

Rubia, K., Alegria, A. A., Cubillo, A. I., Smith, A. B., Brammer, M. J., and Radua, J. (2014). Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Biological Psychiatry*, **76**, 616–628.

Rueda, M. R., Checa, P., and Cómbita, L. M. (2012). Enhanced efficiency of the executive attention network after training in preschool children: Immediate changes and effects after two months. *Developmental Cognitive Neuroscience*, **2**, S192–S204.

Rypma, B., Eldreth, D. A., and Rebbelchi, D. (2007). Age-related differences in activation-performance relations in delayed-response tasks: A multiple component analysis. *Cortex*, **43**, 65–76.

Sacks, O. (1995). *An anthropologist on Mars: Seven paradoxical tales*. New York: Alfred A. Knopf.

Sale, A., et al. (2009). Enrich the environment to empower the brain. *Trends in Neurosciences*, **32**, 233–239.

Salthouse, T. (2012). Consequences of age-related cognitive declines. *Annual Review of Psychology*, **63**, 201–226.

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology*, **54**, 35–54.

Samanez-Larkin, G. R., Robertson, E. R., Mikels, J. A., Carstensen, L. L., and Gotlib, I. H. (2009). Selective attention to emotion in the aging brain. *Psychology and Aging*, **24**, 519–529.

Sammons, R. P., and Keck, T. (2015). Adult plasticity and cortical reorganization after

peripheral lesions. *Current Opinion in Neurobiology*, **35**, 136–141.

Sandin, S., Hultman, C. M., Kolevzon, A., Gross, R., MacCabe, J. H., and Reichenberg, A. (2012). Advancing maternal age is associated with increasing risk for autism: A review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, **51**, 477–486.

Scerri, T. S., and Schulte-Körne, G. (2010). Genetics of developmental dyslexia. *European Child and Adolescent Psychiatry*, **19**, 179–197.

Schmiedek, F., Lövdén, M., and Lindenberger, U. (2010). Hundred days of cognitive training enhance broad cognitive abilities in adulthood: Findings from the COGITO study. *Frontiers in Aging Neuroscience*, **2**, 27.

Schnack, H. G., van Haren, N. E. M., Brouwer, R. M., Evans, A., Durston, S., Boomsma, D. I., et al. (2015). Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cerebral Cortex*, **25**, 1608–1617.

Schoups, A., Vogels, R., Qian, N., and Orban, G. (2001). Practising orientation identification improves orientation coding in V1 neurons. *Nature*, **412**, 549–553.

Schumann, C. M., Bloss, C. S., Barnes, C. C., Wideman, G. M., Carper, R. A., Akshoomoff, N., Courchesne, E., et al. (2010). Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *Journal of Neuroscience*, **30**, 4419–4427.

Sergeant, J. A. (2005). Modeling attention-deficit/hyperactivity disorder: A critical appraisal of the cognitive-energetic model. *Biological Psychiatry*, **57**, 1248–1255.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al. (2006). Intellectual ability and cortical development in children and adolescents. *Nature*, **440**, 676–679.

Shaw, P., Lerch, J., Greenstein, D., Sharp, W., Clasen, L., Evans, A., et al. (2006). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, **63**, 540–549.

Shaw, P., Malek, M., Watson, B., Greenstein, D., de Rossi, P., and Sharp, W. (2013). Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, **74**, 599–606.

Shen, M. D., Nordahl, C. W., Young, G. S., Wootton-Gorges, S. L., Lee, A., Liston, S. E., Amaral, D. G., et al. (2013). Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. *Brain*, **136**, 2825–2835.

Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., and Nelson, C. A. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proceedings of the National Academy of Sciences*, **109**, 12927–12932.

Shi, Y., Kirwan, P., Smith, J., MacLean, G., Orkin, S. H., and Livesey, F. J. (2012). A human stem cell model of early Alzheimer's disease pathology in Down syndrome. *Science Translational Medicine*, **4**(124), 124ra29.

Shiell, M. M., Champoux, F., and Zatorre, R. J. (2014). Enhancement of visual motion detection thresholds in early deaf people. *PloS ONE*, **9**, e90498.

Shulman, E. P., Smith, A. R., Silva, K., Icenogle, G., Duell, N., Chein, J., and Steinberg, L. (2016). The dual systems model: Review, reappraisal, and reaffirmation. *Developmental Cognitive Neuroscience*, **17**, 103–117.

Silbereis, J. C., Pochareddy, S., Zhu, Y., Li, M., and Sestan, N. (2016). The cellular and molecular landscapes of the developing human central nervous system. *Neuron*, **89**, 248–268.

Simmonds, D. J., Hallquist, M. N., Asato, M., and Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *Neuroimage*, **92**, 356–368.

Siuda-Krzywicka, K., Bola, Ł., Paplin'ska, M., Sumera, E., Jednoróg, K., Marchewka, A., Szwed, M., et al. (2016). Massive cortical reorganization in sighted Braille readers. *eLife*, **5**, e10762.

Skeide, M. A., Kraft, I., Müller, B., Schaadt, G., Neef, N., Brauer, J., Friederici, A. D., et al. (2016). NRSN1 associated grey matter volume of the visual word form area reveals dyslexia before school. *Brain*, e-publication in advance of print.

Smit, D. J., Boersma, M., Schnack, H. G., Micheloyannis, S., Boomsma, D. I., Pol, H. E. H., de Geus, E. J., et al. (2012). The brain matures with stronger functional connectivity and decreased randomness of its network. *PLoS ONE*, **7**, e36896.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., and Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, **269**, 107–117.

Somerville, L. H. (2013). The teenage brain: Sensitivity to social evaluation. *Current Directions in Psychological Science*, **22**, 121–127.

Somerville, L. H., Hare, T., and Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of Cognitive Neuroscience*, **23**, 2123–2134.

Sonuga-Barke, E. J. S., Sergeant, J. A., Nigg, J., and Willcutt, E. (2008). Executive dysfunction and delay aversion in attention deficit hyperactivity disorder: Nosologic and diagnostic implications. *Child and Adolescent Psychiatric Clinics of North America*, **17**, 367–84

Sperling, A. J., Lu, Z.-L., Manis, F. R., and Seidenberg, M. S. (2005). Deficits in perceptual noise exclusion in developmental dyslexia. *Nature Neuroscience*, **8**, 862–863.

Spreng, R. N., Stevens, W. D., Viviano, J. D., and Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: Evidence from task and rest. *Neurobiology of Aging*, **45**, 149–160.

Steele, C. J., Bailey, J. A., Zatorre, R. J., and Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: Evidence for a sensitive period. *Journal of Neuroscience*, **33**, 1282–1290.

Stehr-Green, P., Tull, P., Stellfeld, M., Mortenson, P.-B., and Simpson, D. (2003). Autism and thimerosal-containing vaccines: Lack of consistent evidence for an association. *American Journal of Preventive Medicine*, **25**, 101–106.

Stein, J., Talcott, J., and Walsh, V. (2000). Controversy about the visual magnocellular deficit in developmental dyslexics. *Trends in Cognitive Sciences*, **4**, 209–211.

Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends in Cognitive Sciences*, **9**, 69–74.

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental Review*, **28**, 78–106.

Steinberg, L. (2013). The influence of neuroscience on US Supreme Court decisions about adolescents' criminal culpability. *Nature Reviews Neuroscience*, **14**, 513–518.

Stergiakouli, E., Hamshere, M., Holmans, P., Langley, K., Zaharieva, I., Hawi, Z., O'Donovan, M., et al. (2012). Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD. *The American Journal of Psychiatry*, **169**, 186–194.

Stiles, J., Reilly, J., Paul, B., and Moses, P. (2005). Cognitive development following early brain injury: Evidence for neural adaptation. *Trends in Cognitive Sciences*, **9**, 136–143.

Stiles-Davis, J., et al. (1988). Drawing ability in four young children with congenital unilateral brain lesions. *Neuropsychologia*, **26**.

Symonds, G. P. (1937). Mental disorder following head injury. *Proceedings of the Royal Society of Medicine*, **30**, 1081–1094.

Teuber, H. L., and Rudel, R. G. (1962). Behavior after cerebral lesions in children and adults. *Developmental Medicine and Child Neurology*, **3**, 3–20.

Thapar, A., and Cooper, M. (2016). Attention deficit hyperactivity disorder. *Lancet*, **387**(10024), 1240–1250.

Thomas, R., Sanders, S., Doust, J., Beller, E., and Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Pediatrics*, **135**, e994–e1001.

Thompson, P. M., Giedd, J. N., Woods, R. P., MacDonald, D., Evans, A. C., and Toga, A. W. (2000). Growth patterns in the developing brain detected by using continuum mechanical tensor maps. *Nature*, **404**, 190–193.

Tobey, E. A., Thal, D., Niparko, J. K., Eisenberg, L. S., Quittner, A. L., and Wang, N. Y. (2013). Influence of implantation age on school-age language performance in pediatric cochlear implant users. *International Journal of Audiology*, **52**, 219–229.

Toga, A. W., Thompson, P. M., and Sowell, E. R. (2006). Mapping brain maturation. *Trends in Neurosciences*, **29**, 148–159.

Trachtenberg, J. T. (2015). Competition, inhibition, and critical periods of cortical plasticity. *Current Opinion in Neurobiology*, **35**, 44–48.

Treit, S., Lebel, C., Baugh, L., Rasmussen, C., Andrew, G., and Beaulieu, C. (2013). Longitudinal MRI reveals altered trajectory of brain development during childhood and adolescence in fetal alcohol spectrum disorders. *Journal of Neuroscience*, **33**, 10098–10109.

Turner, A. M., and Greenough, W. T. (1985). Differential rearing effects on rat visual cortex synapses: I. Synaptic and neuronal density and synapses per neuron. *Brain Research*, **329**, 195–203.

van der Knapp, M. S. and Valk, J. (1990). MR imaging of the various stages of normal myelination during the first year of life. *Neuroradiology*, **31**, 459–470.

Vandermosten, M., Boets, B., Luts, H., Poelmans, H., Golestani, N., Wouters, J., and Ghesquière, P. (2010). Adults with dyslexia are impaired in categorizing speech and nonspeech sounds on the basis of temporal cues. *Proceedings of the National Academy of Sciences*, **107**, 10389–10394.

Vanderwert, R. E., Zeanah, C. H., Fox, N. A., and Nelson, C. A. (2016). Normalization of EEG activity among previously institutionalized children placed into foster care: A 12-year follow-up of the Bucharest Early Intervention Project. *Developmental Cognitive Neuroscience*, **17**, 68–75.

van Praag, H., Shubert, T., Zhao, C., and Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience*, **25**, 8680–8685.

Veerbeek, J. M., van Wegen, E., van Peppen, R., van der Wees, P. J., Hendriks, E., Rietberg, M., and Kwakkel, G. (2014). What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PloS ONE*, **9**, e87987.

Verbruggen, F., and Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends in Cognitive Sciences*, **12**, 418–424.

Vidyasagar, T. R., and Pammer, K. (2010). Dyslexia: A deficit in visuo-spatial attention, not in phonological processing. *Trends in Cognitive Sciences*, **14**, 57–63.

Vissers, L. E., Gilissen, C., and Veltman, J. A. (2016). Genetic studies in intellectual disability and related disorders. *Nature Reviews Genetics*, **17**, 9–18.

Volkow, N. D., and Swanson, J. M. (2013). Adult attention deficit–hyperactivity disorder. *New England Journal of Medicine*, **369**, 1935–1944.

Waldman, I. D., and Gizer, I. R. (2006). The genetics of attention deficit hyperactivity disorder. *Clinical Psychology Review*, **26**, 396–432.

Wieloch, T., and Nikolic, K. (2006). Mechanisms of neural plasticity following brain injury. *Current Opinion in Neurobiology*, **16**, 258–264.

Wiesel, T. N., and Hubel, D. H. (1963). Single-cell response in striate cortex of kittens deprived of vision in one eye. *Journal of Neurophysiology*, **26**, 1003–1017.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., and Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, **57**, 1336–1346.

Williams, B. M., Luo, Y., Ward, C., Redd, K., Gibson, R., Kuczaj, S. A., and McCoy, J. G. (2001). Environmental enrichment: Effects on spatial memory and hippocampal CREB immunoreactivity. *Physiology and Behavior*, **73**, 649–658.

Wilson, R. S., Bennett, D. A., Bienias, J. L., de Leon, C. M., Morris, M. C., and Evans, D. A. (2003). Cognitive activity and cognitive decline in a biracial community population. *Neurology*, **61**, 812–816.

Wiseman, F. K., Alford, K. A., Tybulewicz, V. L., and Fisher, E. M. (2009). Down syndrome – recent progress and future prospects. *Human Molecular Genetics*, **18**,

R75–R83.

Wolff, J. J., Gu, H., Gerig, G., Ellison, J. T., Styner, M., Gouttard, S., Evans, A. C., et al. (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *American Journal of Psychiatry*, **169**, 589–600.

Wright, L., Lipszyc, J., Dupuis, A., Thayapararajah, S. W., and Schachar, R. (2014). Response inhibition and psychopathology: A meta-analysis of go/no-go task performance. *Journal of Abnormal Psychology*, **123**, 429–439.

Xerri, C. (2012). Plasticity of cortical maps: Multiple triggers for adaptive reorganization following brain damage and spinal cord injury. *The Neuroscientist*, **18**(2), 133–148.

Yuan, P., and Raz, N. (2014). Prefrontal cortex and executive functions in healthy adults: A meta-analysis of structural neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, **42**, 180–192.

Zeiler, S. R., and Krakauer, J. W. (2013). The interaction between training and plasticity in the post-stroke brain. *Current Opinion in Neurology*, **26**, 609–616.

Ziegler, D., Piguet, O., Salat, D., Prince, K., Connally, E., and Corkin, S. (2010). Cognitive ability in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging*, **31**, 1912–1926.

Ziegler, J. C., and Goswami, U. (2005). Reading acquisition, developmental dyslexia, and skilled reading across languages: A psycholinguistic grain size theory. *Psychological Bulletin*, **131**, 3–29.

Zielinski, B. A., Prigge, M. B., Nielsen, J. A., Froehlich, A. L., Abildskov, T. J., Anderson, J. S., Alexander, A. L., et al. (2014). Longitudinal changes in cortical thickness in autism and typical development. *Brain*, **137**, 1799–1812.

Chapter 16

Aarsland, D., Brønnick, K., and Fladby, T. (2011). Mild cognitive impairment in Parkinson's disease. *Current Neurology and Neuroscience Reports*, **11**, 371–378.

Adlard, P. A., Tran, B. A., Finkelstein, D. I., Desmond, P. M., Johnston, L. A., Bush, A. I., and Egan, G. F. (2014). A review of β -amyloid neuroimaging in Alzheimer's disease. *Frontiers in Neuroscience*, **8**, 327.

Algattas, H., and Huang, J. H. (2013). Traumatic brain injury pathophysiology and treatments: Early, intermediate, and late phases post-injury. *International Journal of Molecular Sciences*, **15**, 309–341.

Ali, F., Stott, S. R., and Barker, R. A. (2014). Stem cells and the treatment of Parkinson's disease. *Experimental Neurology*, **260**, 3–11.

Alonso, A., and Hernán, M. A. (2008). Temporal trends in the incidence of multiple sclerosis: A systematic review. *Neurology*, **71**, 129–135.

Alway, Y., Gould, K. R., McKay, A., Johnston, L., and Ponsford, J. (2016). The evolution of post-traumatic stress disorder following moderate-to-severe traumatic brain injury. *Journal of Neurotrauma*, **33**, 825–831.

Alzheimer's Association. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimer's and Dementia*, **12**, 459–509.

Amato, M. P., Langdon, D., Montalban, X., Benedict, R. H., DeLuca, J., Krupp, L. B., Comi, G., et al. (2013). Treatment of cognitive impairment in multiple sclerosis: Position paper. *Journal of Neurology*, **260**, 1452–1468.

American Academy of Neurology. (2008). Position statement on sports that include intentional trauma to the brain.

Anand, P., and Singh, B. (2013). A review on cholinesterase inhibitors for Alzheimer's disease. *Archives of Pharmacal Research*, **36**, 375–399.

Antoniades, C. A., and Watts, C. (2013). Huntington's disease and cell therapies: Past, present, and future. *Trinucleotide Repeat Protocols*, 19–32.

Arendt, T. (2009). Synaptic degeneration in Alzheimer's disease. *Acta Neuropathologica*, **118**, 167–179.

Bachoud-Lévi, A. C., Gaura, V., Brugières, P., Lefaucheur, J. P., Boissé, M. F., Maison, P., Cesaro, P., et al. (2006). Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: A long-term follow-up study. *The Lancet Neurology*, **5**, 303–309.

Barak, Y., and Achiron, A. (2000). Effect of interferon-beta-1b on cognitive functions in multiple sclerosis. *Annals of Neurology*, **48**, 885–892.

Barth, J. T., Alves, W. M., Ryan, T. V., Macchiocchi, S. N., Rimel, R. W., Jane, J. A., and Nelson, W. E. (1989). Mild head injury in sports: Neuropsychological sequelae and recovery of function. In H. S. Levin, H. M. Eisenberg, and A. L. Benton (eds.), *Mild head injury*. New York: Oxford University Press.

Bayles, K. A. (1982). Language function in senile dementia. *Brain and Language*, **16**, 265–280.

Bekinschtein, T. A., Manes, F. F., Villarreal, M., Owen, A. M., and Della Maggiore, V. (2011). Functional imaging reveals movement preparatory activity in the vegetative state. *Frontiers in Human Neuroscience*, **5**, 5.

Belanger, H. G., and Vanderploeg, R. D. (2005). The neuropsychological impact of sports-related concussion: A meta-analysis. *Journal of the International Neuropsychological Society*, **11**, 345–357.

Belbasis, L., Bellou, V., Evangelou, E., Ioannidis, J. P., and Tzoulaki, I. (2015). Environmental risk factors and multiple sclerosis: An umbrella review of systematic reviews and meta-analyses. *The Lancet Neurology*, **14**, 263–273.

Berényi, A., Belluscio, M., Mao, D., and Buzsáki, G. (2012). Closed-loop control of epilepsy by transcranial electrical stimulation. *Science*, **337**, 735–737.

Bertram, L., and Tanzi, R. E. (2008). Thirty years of Alzheimer's disease genetics: The implications of systematic meta-analyses. *Nature Reviews Neuroscience*, **9**, 768–778.

Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., and Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. *BMC Public Health*, **14**, 1.

Binnewijzend, M. A., Schoonheim, M. M., Sanz-Arigita, E., Wink, A. M., van der Flier, W. M., Tolboom, N., Barkhof, F., et al. (2012). Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*, **33**, 2018–2028.

Bogdanova, Y., and Verfaellie, M. (2012). Cognitive sequelae of blast-induced traumatic brain injury: Recovery and rehabilitation. *Neuropsychology Review*, **22**, 4–20.

Bonelli, R. M., and Cummings, J. L. (2008). Frontal-subcortical dementias. *Neurologist*, **14**, 100–107.

Borek, L. L., Amick, M. M., and Friedman, J. H. (2006). Non-motor aspects of Parkinson's disease. *CNS Spectrums*, **11**, 541–554.

Broeders, M., de Bie, R. M. A., Velseboer, D. C., Speelman, J. D., Muslimovic, D., and Schmand, B. (2013). Evolution of mild cognitive impairment in Parkinson disease. *Neurology*, **81**, 346–352.

Brønnick, K., Alves, G., Aarsland, D., Tysnes, O. B., and Larsen, J. P. (2011). Verbal memory in drug-naïve, newly diagnosed Parkinson's disease. The retrieval deficit hypothesis revisited. *Neuropsychology*, **25**, 114–124.

Brunden, K. R., Trojanowski, J. Q., and Lee, V. M.-Y. (2009). Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. *Nature Reviews Drug Discovery*, **8**, 783–793.

Bruno, M. A., Gosseries, O., Ledoux, D., Hustinx, R., and Laureys, S. (2011). Assessment of consciousness with electrophysiological and neurological imaging techniques. *Current Opinion in Critical Care*, **17**, 146–151.

Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: Pathways, pathogenesis and therapy. *Nature Reviews Neuroscience*, **10**, 333–344.

Camp, S. J., Stevenson, V. L., Thompson, A. J., Ingle, G. T., Miller, D. H., Borrás, C., et al. (2005). A longitudinal study of cognition in primary progressive multiple sclerosis. *Brain*, **128**, 2891–2898.

Castro-Borrero, W., Graves, D., Frohman, T. C., Flores, A. B., Hardeman, P., Logan, D., Frohman, E. M., et al. (2012). Current and emerging therapies in multiple sclerosis: A systematic review. *Therapeutic Advances in Neurological Disorders*, **5**, 205–220.

Chen, A. J. W., and D'Esposito, M. (2010). Traumatic brain injury: From bench to bedside to society. *Neuron*, **66**, 11–14.

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., and Ganguli, M. (2000). Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology*, **55**, 1847–1853.

Chiaravalloti, N. D., and DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology*, **7**, 1139–1151.

Clancy, M. J., Clarke, M. C., Connor, D. J., Cannon, M., and Cotter, D. R. (2014). The prevalence of psychosis in epilepsy: A systematic review and meta-analysis. *BMC Psychiatry*, **14**, 1.

Clark, M. D., Asken, B. M., Marshall, S. W., and Guskiewicz, K. M. (2017). Descriptive characteristics of concussions in National Football League games, 2010–2011 to 2013–2014. *The American Journal of Sports Medicine*, e-publication in advance of print.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., and Owen, A. M. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, **130**, 2494–2507.

Comi, G. (2009). Shifting the paradigm toward earlier treatment of multiple sclerosis with interferon beta. *Clinical Therapeutics*, **31**, 1142–1157.

Connick, P., Kolappan, M., Crawley, C., Webber, D. J., Patani, R., Michell, A. W., Compston, A., et al. (2012). Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: An open-label phase 2a proof-of-concept study. *The Lancet Neurology*, **11**, 150–156.

Cremona-Meteyard, S. L., and Geffen, G. M. (1994). Persistent visuospatial attention deficits following mild head injury in Australian Rules football players. *Neuropsychologia*, **32**, 649–662.

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., Owen, A. M., et al. (2012). Bedside detection of awareness in the vegetative state: A cohort study. *The Lancet*, **378**, 2088–2094.

Davis, D. P., Serrano, J. A., Vilke, G. M., Sise, M. J., Kennedy, F., Eastman, B., et al. (2006). The predictive value of field versus arrival Glasgow Coma Scale score and TRISS calculations in moderate-to-severe traumatic brain injury. *Journal of Trauma*

Injury, Infection, and Critical Care, **60**, 985–990.

Demertzi, A., Soddu, A., and Laureys, S. (2013). Consciousness supporting networks. *Current Opinion in Neurobiology*, **23**, 239–244.

Dennis, E. L., and Thompson, P. M. (2014). Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychology Review*, **24**, 49–62.

Derry, C. P., and Duncan, S. (2013). Sleep and epilepsy. *Epilepsy and Behavior*, **26**, 394–404.

Deshmukh, V. A., Tardif, V., Lyssiotis, C. A., Green, C. C., Kerman, B., Kim, H. J., Gage, F. H., et al. (2013). A regenerative approach to the treatment of multiple sclerosis. *Nature*, **502**, 327–332.

Deuschl, G., Scade-Brittinger, C., Krack, P., Volkmann, J., et al. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, **355**, 896–908.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, **68**, 895–899.

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., et al. (2009). The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cerebral Cortex*, **19**, 497–510.

Dirnberger, G., and Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: A review. *Journal of Neuropsychology*, **7**, 193–224.

Donix, M., Burggren, A. C., Suthana, N. A., Siddarth, P., Ekstrom, A. D., Krupa, A. K., Small, G. W., et al. (2010). Family history of Alzheimer's Disease and hippocampal

structure in healthy people. *American Journal of Psychiatry*, **167**, 1399–1406.

Donix, M., Small, G. W., and Bookheimer, S. Y. (2012). Family history and APOE-4 genetic risk in Alzheimer's disease. *Neuropsychology Review*, **22**, 298–309.

Drzezga, A., Grimmer, T., Henriksen, G., Muhlau, M., Perneczky, R., Miederer, I., et al. (2009). Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. *Neurology*, **72**, 1487–1494.

Du, A.-T., Schuff, N., Kramer, J. H., Rosen, H. J., Gorno-Tempini, M. L., Rankin, K., et al. (2007). Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain*, **130**, 1159–1166.

Duff, K., Paulsen, J., Mills, J., Beglinger, L. J., Moser, D. J., Smith, M. M., et al. and PREDICT-HD Investigators. (2010). Mild cognitive impairment in prediagnosed Huntington disease. *Neurology*, **75**, 500–507.

Elder, G. A., and Cristian, A. (2009). Blast-related mild traumatic brain injury: Mechanisms of injury and impact on clinical care. *Mount Sinai Journal of Medicine*, **76**, 111–118.

Estraneo, A., Moretta, P., Loreto, V., Lanzillo, B., Santoro, L., and Trojano, L. (2010). Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. *Neurology*, **75**, 239–245.

Farbota, K. D., Bendlin, B. B., Alexander, A. L., Rowley, H. A., Dempsey, R. J., and Johnson, S. C. (2012). Longitudinal diffusion tensor imaging and neuropsychological correlates in traumatic brain injury patients. *Frontiers in Human Neuroscience*, **6**, 160.

Fasano, A., Daniele, A., and Albanese, A. (2012). Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *The Lancet Neurology*, **11**, 429–442.

Faul, M., and Coronado, V. (2014). Epidemiology of traumatic brain injury. *Handbook of Clinical Neurology*, **127**, 3–13.

Faul, M., Xu, L., Wald, M. M., Coronado, V. G. (2010). Traumatic brain injury in the United States: Emergency department visits, hospitalizations and deaths, 2002–2006. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Ferlisi, M., and Shorvon, S. (2014). Seizure precipitants (triggering factors) in patients with epilepsy. *Epilepsy and Behavior*, **33**, 101–105.

Fernández-Espejo, D., Bekinschtein, T., Monti, M. M., Pickard, J. D., Junque, C., Coleman, M. R., and Owen, A. M. (2011). Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. *Neuroimage*, **54**, 103–112.

Filippi, M., Agosta, F., Spinelli, E. G., and Rocca, M. A. (2013). Imaging resting state brain function in multiple sclerosis. *Journal of Neurology*, **260**, 1709–1713.

Fischer, J. S., Priore, R. L., Jacobs, L. D., Cookfair, D. L., Rudick, R. A., Herndon, R. M., et al. (2000). Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Annals of Neurology*, **48**, 885–892.

Folstein, M. F., Folstein, S. E., McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

Foran, A., Bowden, S., Bardenhagen, F., Cook, M., and Meade, C. (2013). Specificity of psychopathology in temporal lobe epilepsy. *Epilepsy and Behavior*, **27**, 193–199.

Frisch, S., Dukart, J., Vogt, B., Horstmann, A., Becker, G., Villringer, A., Schroeter, M. L., et al. (2013). Dissociating memory networks in early Alzheimer's disease and

frontotemporal lobar degeneration: A combined study of hypometabolism and atrophy. *PloS ONE*, **8**, e55251.

Fuentes, P. (2009). Current anti-dementia drugs: Hypothesis and clinical benefits. In R. B. Maccioni and G. Perry (eds.), *Current hypotheses and research milestones in Alzheimer's disease* (pp. 237–241). New York: Springer.

Galarneau, M. R., Woodruff, S. I., Dye, J. L., Mohrle, C. R., and Wade, A. L. (2008). Traumatic brain injury during Operation Iraqi Freedom: Findings from the United States Navy-Marine Corps Combat Trauma Registry. *Journal of Neurosurgery*, **108**, 950–957.

Gale, S. D., Johnson, S. C., Bigler, E. D., and Blatter, D. D. (1995). Nonspecific white matter degeneration following traumatic brain injury. *Journal of the International Neuropsychological Society*, **1**, 26.

Ganguli, M., Snitz, B. E., Saxton, J. A., Chang, C. C. H., Lee, C. W., Vander Bilt, J., Petersen, R. C., et al. (2011). Outcomes of mild cognitive impairment by definition: A population study. *Archives of Neurology*, **68**, 761–767.

Georgiou-Karistianis, N., Stout, J., Poudel, G., Gray, M., Dominguez, J., Churchyard, A., Egan, G., et al. (2012). A05 Longitudinal functional and connectivity changes during working memory performance in Huntington's disease: The image-HD study. *Journal of Neurology, Neurosurgery and Psychiatry*, **83**(Suppl. 1), A2–A2.

Giza, C. C., Kutcher, J. S., Ashwal, S., Barth, J., Getchius, T. S., Gioia, G. A., McKeag, D. B., et al. (2013). Summary of evidence-based guideline update: Evaluation and management of concussion in sports Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, **80**, 2250–2257.

Gourraud, P. A., Harbo, H. F., Hauser, S. L., and Baranzini, S. E. (2012). The genetics of multiple sclerosis: An up-to-date review. *Immunological Reviews*, **248**, 87–103.

Graham, R., Rivara, F. P., Ford, M. A., Spicer, C. M., Institute of Medicine, and

National Research Council. (2014). Sports-related concussions in youth: Improving the science, changing the culture. Washington, DC: National Academies Press.

Helmick, K. M., Spells, C. A., Malik, S. Z., Davies, C. A., Marion, D. W., and Hinds, S. R. (2015). Traumatic brain injury in the US military: Epidemiology and key clinical and research programs. *Brain Imaging and Behavior*, **9**, 358–366.

Henley, S. M., Novak, M. J., Frost, C., King, J., Tabrizi, S. J., and Warren, J. D. (2012). Emotion recognition in Huntington's disease: A systematic review. *Neuroscience and Biobehavioral Reviews*, **36**, 237–253.

Hind, D., Cotter, J., Thake, A., Bradburn, M., Cooper, C., Isaac, C., and House, A. (2014). Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: A systematic review and meta-analysis. *BMC Psychiatry*, **14**, 1.

Hogan, D. B., Jetté, N., Fiest, K. M., Roberts, J. I., Pearson, D., Smith, E. E., Maxwell, C. J., et al. (2016). The prevalence and incidence of frontotemporal dementia: A systematic review. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, **43**, S96–S109.

Holsinger, T., Steffens, D. C., Phillips, C., Helms, M., Havlik, R. J., Brietner, J. C. S., et al. (2002). Head injury in early adulthood and the lifetime risk of depression. *Archives of General Psychiatry*, **59**, 17–22.

Hoppe, C., and Elger, C. E. (2011). Depression in epilepsy: A critical review from a clinical perspective. *Nature Reviews Neurology*, **7**, 462–472.

Hornberger, M., and Piguet, O. (2012). Episodic memory in frontotemporal dementia: A critical review. *Brain*, **135**, 678–692.

Hoth, K. F., Paulsen, J. S., Moser, D. J., Tranel, D., Clark, L. A., and Bechara, A. (2007). Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. *Journal of Clinical and Experimental*

Neuropsychology, **29**, 365–376.

Howard, R., McShane, R., Lindesay, J., Ritchie, C., Baldwin, A., Barber, R., Jones, R., et al. (2015). Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: Secondary and post-hoc analyses. *The Lancet Neurology*, **14**, 1171–1181.

Huang, C., Mattis, P., Tang, C., Perrine, K., Carbon, M., and Eidelberg, D. (2007). Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage*, **34**, 714–723.

Hulkower, M. B., Poliak, D. B., Rosenbaum, S. B., Zimmerman, M. E., and Lipton, M. L. (2013). A decade of DTI in traumatic brain injury: 10 years and 100 articles later. *American Journal of Neuroradiology*, **34**, 2064–2074.

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron*, **80**, 844–866.

Inglese, M., Ge, Y., Filippi, M., Falini, A., Grossman, R. I., and Gonen, O. (2004). Indirect evidence for early widespread gray matter involvement in relapsing-remitting multiple sclerosis. *NeuroImage*, **21**, 1825–1829.

Irwin, D. J., Lee, V. M. Y., and Trojanowski, J. Q. (2013). Parkinson's disease dementia: Convergence of α -synuclein, tau and amyloid- β pathologies. *Nature Reviews Neuroscience*, **14**, 626–636.

Jacobs, D. M., Levy, G., and Marder, K. (2006). Dementia in Parkinson's disease, Huntington's disease, and related disorders. In M. J. Farah and T. E. Feinberg (eds.), *Patient-based approaches to cognitive neuroscience* (2nd edn.) (pp. 381–395). Cambridge, MA: MIT Press.

Jagust, W. (2016). Is amyloid- β harmful to the brain? Insights from human imaging studies. *Brain*, **139**, 23–30.

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues in Clinical Neuroscience*, **15**, 445–454.

Jette, N., and Wiebe, S. (2013). Update on the surgical treatment of epilepsy. *Current Opinion in Neurology*, **26**, 201–207.

Jordan, B. D. (2013). The clinical spectrum of sport-related traumatic brain injury. *Nature Reviews Neurology*, **9**, 222–230.

Julien, C. L., Thompson, J. C., Wild, S., Yardumian, P., Snowden, J. S., Turner, G., and Craufurd, D. (2007). Psychiatric disorders in preclinical Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **78**, 939–943.

Kalmar, J. H., Gaudino, E. A., Moore, N. B., Halper, J., and DeLuca, J. (2008). The relationship between cognitive deficits and everyday functional activities in multiple sclerosis. *Neuropsychology*, **22**, 442–449.

Kamm, C. P., Uitdehaag, B. M., and Polman, C. H. (2014). Multiple sclerosis: Current knowledge and future outlook. *European Neurology*, **72**, 132–141.

Karp, A., Paillard-Borg, S., Wang, H. X., Silverstein, M., Winblad, B., and Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders*, **21**, 65–73.

Karr, J. E., Areshenkoff, C. N., and Garcia-Barrera, M. A. (2014). The neuropsychological outcomes of concussion: A systematic review of meta-analyses on the cognitive sequelae of mild traumatic brain injury. *Neuropsychology*, **28**, 321–336.

Kehagia, A. A., Barker, R. A., and Robbins, T. W. (2010). Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *The Lancet Neurology*, **9**, 1200–1213.

King, D., Brughelli, M., Hume, P., and Gissane, C. (2014). Assessment, management and knowledge of sport-related concussion: Systematic review. *Sports Medicine*, **44**, 449–471.

Kotchoubey, B. (2009). Vegetative state. In L. R. Squire (ed.), *Encyclopedia of neuroscience* (pp. 61–66). Oxford: Academic Press.

Kotchoubey, B., Merz, S., Lang, S., Markl, A., Müller, F., Yu, T., and Schwarzbauer, C. (2013). Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. *Journal of Neurology*, **260**, 975–983.

Krook-Magnuson, E., Armstrong, C., Oijala, M., and Soltesz, I. (2013). On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. *Nature Communications*, **4**, 1376.

Kucera, K. L. (2017). Traumatic brain and spinal cord fatalities among high school and college football players – United States, 2005–2014. *MMWR. Morbidity and Mortality Weekly Report*, **65**.

Launer, L. J., Petrovitch, H., Ross, G. W., Markesbery, W., and White, L. R. (2008). AD brain pathology: Vascular origins? Results from the HAAS autopsy study. *Neurobiology of Aging*, **29**, 1587–1590.

Laureys, S., Celesia, G. G., Cohadon, F., Lavrijsen, J., León-Carrión, J., Sannita, W. G., Dolce, G., et al. (2010). Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome. *BMC Medicine*, **8**, 1.

Lee, Y. K., Hou, S. W., Lee, C. C., Hsu, C. Y., Huang, Y. S., and Su, Y. C. (2013). Increased risk of dementia in patients with mild traumatic brain injury: A nationwide cohort study. *PloS ONE*, **8**, e62422.

Lehman, E. J., Hein, M. J., Baron, S. L., and Gersic, C. M. (2012). Neurodegenerative causes of death among retired National Football League players. *Neurology*, **79**,

1970–1974.

Lindvall, O., and Kokaia, Z. (2009). Prospects of stem cell therapy for replacing dopamine neurons in Parkinson's disease. *Trends in Pharmacological Sciences*, **30**, 260–267.

Liu, F., Wang, Y., Li, M., Wang, W., Li, R., Zhang, Z., et al. (2017). Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Human Brain Mapping*, **38**(2), 957–973.

Löscher, W., Gernert, M., and Heinemann, U. (2008). Cell and gene therapies in epilepsy: Promising avenues or blind alleys? *Trends in Neurosciences*, **31**, 62–73.

Lott, I. T., and Dierssen, M. (2010). Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *The Lancet Neurology*, **9**, 623–633.

Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I. A., Ukoumunne, O. C., and Llewellyn, D. J. (2013). Mediterranean diet, cognitive function, and dementia: A systematic review. *Epidemiology*, **24**, 479–489.

Loy, C. T., Schofield, P. R., Turner, A. M., and Kwok, J. B. (2014). Genetics of dementia. *The Lancet*, **383**, 828–840.

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Tamjeedi, R., Monchi, O., Ganjavi, H., and MacDonald, P. A. (2013). Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. *PloS ONE*, **8**, e74044.

Mahurin, R. K. (2008). Frontal-subcortical determinants of processing speed in Parkinson's disease. In J. DeLuca and J. Kalmar (eds.), *Information processing speed in clinical populations* (pp. 195–220). New York: Taylor and Francis.

Majdan, M., Steyerberg, E. W., Nieboer, D., Mauritz, W., Rusnak, M., and Lingsma,

H. F. (2015). Glasgow coma scale motor score and pupillary reaction to predict six-month mortality in patients with traumatic brain injury: Comparison of field and admission assessment. *Journal of Neurotrauma*, **32**, 101–108.

Marshman, L. A., Jakabek, D., Hennessy, M., Quirk, F., and Guazzo, E. P. (2013). Post-traumatic amnesia. *Journal of Clinical Neuroscience*, **20**, 1475–1481.

Martland, H. (1928). Punch drunk. *JAMA*, **91**, 1103–1107.

Mathias, J. L., and Burke, J. (2009). Cognitive functioning in Alzheimer's and vascular dementia: A meta-analysis. *Neuropsychology*, **23**, 411–423.

Matute, C., and Pérez-Cerdá, F. (2005). Multiple sclerosis: Novel perspectives on newly forming lesions. *Trends in Neurosciences*, **28**, 173–175.

McCrea, M., Guskiewicz, K., Randolph, C., Barr, W. B., Hammeke, T. A., Marshall, S. W., Kelly, J. P., et al. (2013). Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes. *Journal of the International Neuropsychological Society*, **19**, 22–33.

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvorák, J., Echemendia, R. J., Sills, A., et al. (2013). Consensus statement on concussion in sport: The 4th International Conference on Concussion in Sport held in Zurich, November 2012. *British Journal of Sports Medicine*, **47**, 250–258.

McCrory, P., Zazryn, T., and Cameron, P. (2007). The evidence for chronic traumatic encephalopathy in boxing. *Sports Medicine*, **37**, 467–476.

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., Riley, D. O., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, **136**, 43–64.

Mendez, M. F. (2006). Frontotemporal dementia. In M. J. Farah and T. E. Feinberg

(eds.), *Patient-based approaches to cognitive neuroscience* (2nd edn.) (pp. 371–379). Cambridge, MA: MIT Press.

Menon, D. K., Owen, A. M., Williams, E. J., Minhas, P. S., Allen, C. M. C., Boniface, S. J., Pickard, J. D., and Wolfson Brain Imaging Centre Team. (1998). Cortical processing in persistent vegetative state. *Lancet*, **352**, 200.

Menon, D. K., Schwab, K., Wright, D. W., and Maas, A. I. (2010). Position statement: Definition of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, **91**, 1637–1640.

Mesulam, M. (2013). Cholinergic circuitry of the human nucleus basalis and its fate in Alzheimer's disease. *Journal of Comparative Neurology*, **521**, 4124–4144.

Mesulam, M. M., Weintraub, S., Rogalski, E. J., Wieneke, C., Geula, C., and Bigio, E. H. (2014). Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. *Brain*, **137**, 1176–1192.

Mez, J., Stern, R. A., and McKee, A. C. (2013). Chronic traumatic encephalopathy: Where are we and where are we going? *Current Neurology and Neuroscience Reports*, **13**, 1–12.

Minati, L., Edginton, T., Bruzzone, M. G., and Giaccone, G. (2009). Current concepts in Alzheimer's disease: A multidisciplinary review. *American Journal of Alzheimer's Disease and Other Dementias*, **24**, 95–121.

Monti, M. M., Vanhaudenhuyse, A., Coleman, M. R., Boly, M., Pickard, J. D., Tshibanda, L., Laureys, S., et al. (2010). Willful modulation of brain activity in disorders of consciousness. *New England Journal of Medicine*, **362**, 579–589.

Montoya, A., Price, B. H., Menear, M., and Lepage, M. (2006). Brain imaging and cognitive dysfunctions in Huntington's disease. *Journal of Psychiatry and Neuroscience*, **31**, 21–29.

Mortimer, J. A., and Pirozzolo, F. J. (1985). Remote effects of head trauma. *Developmental Neuropsychology*, **1**, 215–229.

Mula, M. (2013). The interictal dysphoric disorder of epilepsy: A still open debate. *Current Neurology and Neuroscience Reports*, **13**, 1–6.

Myers, N., Pasquini, L., Göttler, J., Grimmer, T., Koch, K., Ortner, M., Förstl, H., et al. (2014). Within-patient correspondence of amyloid- β and intrinsic network connectivity in Alzheimer's disease. *Brain*, **137**, 2052–2064.

Narayanan, N. S., Rodnitzky, R. L., and Uc, E. Y. (2013). Prefrontal dopamine signaling and cognitive symptoms of Parkinson's disease. *Reviews in the Neurosciences*, **24**, 267–278.

Narme, P., Mouras, H., Roussel, M., Duru, C., Krystkowiak, P., and Godefroy, O. (2013). Emotional and cognitive social processes are impaired in Parkinson's disease and are related to behavioral disorders. *Neuropsychology*, **27**, 182–192.

Nassery, A., Palmese, C. A., Sarva, H., Groves, M., Miravite, J., and Kopell, B. H. (2016). Psychiatric and cognitive effects of deep brain stimulation for Parkinson's disease. *Current Neurology and Neuroscience Reports*, **16**, 87.

Nickels, K. C., Zaccariello, M. J., Hamiwka, L. D., and Wirrell, E. C. (2016). Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. *Nature Reviews Neurology*, **12**, 465–476.

Noble, J. M., and Hesdorffer, D. C. (2013). Sport-related concussions: A review of epidemiology, challenges in diagnosis, and potential risk factors. *Neuropsychology Review*, **23**, 273–284.

Noonan, W. C. W., Kathman, S. J., and White, C. M. C. (2002). Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology*, **58**,

136–138.

Novak, M. J., and Tabrizi, S. J. (2010). Huntington's disease. *BMJ*, **340**.

Noyce, A. J., Bestwick, J. P., Silveira-Moriyama L., et al. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Annals of Neurology*, **72**, 893–901.

O'Brien, J., and Thomas, A. (2015). Vascular dementia. *The Lancet*, **386**, 1698–1706.

O'Callaghan, C., Hodges, J. R., and Hornberger, M. (2013). Inhibitory dysfunction in frontotemporal dementia: A review. *Alzheimer Disease and Associated Disorders*, **27**, 102–108.

Oksenberg, J. R., Baranzini, S. E., Sawcer, S., and Hauser, S. L. (2008). The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. *Nature Reviews Genetics*, **9**, 516–526.

Owen, A. M., and Coleman, M. R. (2008). Functional neuroimaging of the vegetative state. *Nature Reviews Neuroscience*, **9**, 235–243.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., and Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, **313**, 1402.

Papp, K. V., Kaplan, R. F., and Snyder, P. J. (2011). Biological markers of cognition in prodromal Huntington's disease: A review. *Brain and Cognition*, **77**, 280–291.

Parisi, P., Bruni, O., Pia Villa, M., Verrotti, A., Miano, S., Luchetti, A., and Curatolo, P. (2010). The relationship between sleep and epilepsy: The effect on cognitive functioning in children. *Developmental Medicine and Child Neurology*, **52**, 805–810.

Paulsen, J. S. (2011). Cognitive impairment in Huntington disease: Diagnosis and treatment. *Current Neurology and Neuroscience Reports*, **11**, 474–483.

Paulsen, J. S., Langbehn, D. R., Stout, J. C., et al. (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery, and Psychiatry*, **79**, 874–880.

Paulsen, J. S., Nehl, C., Hoth, K. F., Kanz, J. E., Benjamin, M., Conybeare, R., Turner, B., et al. (2005). Depression and stages of Huntington's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, **17**, 496–502.

Perl, D. P. (2010). Neuropathology of Alzheimer's disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*, **77**, 32–42.

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., and Fratiglioni, L. (2014). Mild cognitive impairment: A concept in evolution. *Journal of Internal Medicine*, **275**, 214–228.

Petersen, R. C. and Negash, S. (2008). Mild cognitive impairment: An overview. *CNS Spectrums*, **13**, 45–53.

Pfister, T., Pfister, K., Hagel, B., Ghali, W. A., and Ronksley, P. E. (2016). The incidence of concussion in youth sports: A systematic review and meta-analysis. *British Journal of Sports Medicine*, **50**, 292–297.

Pievani, M., de Haan, W., Wu, T., Seeley, W. W., and Frisoni, G. B. (2011). Functional network disruption in the degenerative dementias. *The Lancet Neurology*, **10**, 829–843.

Politis, M., and Lindvall, O. (2012). Clinical application of stem cell therapy in Parkinson's disease. *BMC Medicine*, **10**, 1.

Ponsford, J., Bayley, M., Wiseman-Hakes, C., Togher, L., Velikonja, D., McIntyre, A., Tate, R., et al. (2014). INCOG recommendations for management of cognition following traumatic brain injury, part II: Attention and information processing speed. *Journal of Head Trauma Rehabilitation*, **29**, 321–337.

Rademakers, R., Neumann, M., and Mackenzie, I. R. (2012). Advances in understanding the molecular basis of frontotemporal dementia. *Nature Reviews Neurology*, **8**, 423–434.

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Neville, B. G., et al. (2014). Neurobehavioral comorbidities in children with active epilepsy: A population-based study. *Pediatrics*, **133**, e1586–e1593.

Reisberg, B., Ferris, S. H., deLeon, M. J., and Crook, T. (1988). Global Deterioration Scale (GDS). *Psychopharmacology Bulletin*, **24**, 661–663.

Reisberg, B., Ferris, S. H., deLeon, M. J., Kluger, A., Franssen, E., Borenstein, J., and Alba, R. C. (1989). The stage-specific temporal course of Alzheimer's disease: Functional and behavioral concomitants based upon cross-sectional and longitudinal observation. *Progress in Clinical and Biological Research*, **317**, 23–41.

Rentz, D. M., Rodriguez, M. A. P., Amariglio, R., Stern, Y., Sperling, R., and Ferris, S. (2013). Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: A selective review. *Alzheimer's Research and Therapy*, **5**, 1.

Rice, C. M., Kemp, K., Wilkins, A., and Scolding, N. J. (2013). Cell therapy for multiple sclerosis: An evolving concept with implications for other neurodegenerative diseases. *The Lancet*, **382**, 1204–1213.

Riggio, S., and Wong, M. (2009). Neurobehavioral sequelae of traumatic brain injury. *Mount Sinai Journal of Medicine*, **76**, 163–172.

Roberts, R. O., Knopman, D. S., Mielke, M. M., Cha, R. H., Pankratz, V. S., Christianson, T. J., Rocca, W. A., et al. (2014). Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. *Neurology*, **82**, 317–325.

Rocca, M. A., Amato, M. P., de Stefano, N., Enzinger, C., Geurts, J. J., Penner, I. K., et al. and MAGNIMS Study Group. (2015). Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *The Lancet Neurology*, **14**, 302–317.

Roper, S. N., and Steindler, D. A. (2013). Stem cells as a potential therapy for epilepsy. *Experimental Neurology*, **244**, 59–66.

Rosas, H. D., Salat, D. H., Lee, S. Y., Zaleta, A. K., Pappu, V., Fischl, B., et al. (2008). Cerebral cortex and the clinical expression of Huntington's disease: Complexity and heterogeneity. *Brain*, **131**, 1057–1068.

Rosenfeld, J. V., Maas, A. I., Bragge, P., Morganti-Kossmann, M. C., Manley, G. T., and Gruen, R. L. (2012). Early management of severe traumatic brain injury. *The Lancet*, **380**, 1088–1098.

Rosenfeld, J. V., McFarlane, A. C., Bragge, P., Armonda, R. A., Grimes, J. B., and Ling, G. S. (2013). Blast-related traumatic brain injury. *The Lancet Neurology*, **12**(9), 882–893.

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Reilmann, R., et al. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology*, **10**, 204–216.

Rovaris, M., Judica, E., Gallo, A., Benedetti, B., Sormani, M. P., Caputo, D., et al. (2006). Grey matter damage predicts the evolution of primary progressive multiple sclerosis at 5 years. *Brain*, **129**, 2628–2634.

Rowland, L. P. (2006). Why haven't we banned boxing? *Neurology Today*, **6**, 5–6.

Salmond, C. H., Menon, D. K., Chatfield, D. A., Williams, G. B., Pena, A., Sahakian, B. J., and Pickard, J. D. (2006). Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *Neuroimage*, **29**(1),

117–124.

Salomone, S., Caraci, F., Leggio, G. M., Fedotova, J., and Drago, F. (2012). New pharmacological strategies for treatment of Alzheimer's disease: Focus on disease modifying drugs. *British Journal of Clinical Pharmacology*, **73**, 504–517.

Savica, R., Parisi, J. E., Wold, L. E., Josephs, K. A., and Ahlskog, J. E. (2012). High school football and risk of neurodegeneration: A community-based study. *Mayo Clinic Proceedings*, **87**, 335–340.

Sbardella, E., Petsas, N., Tona, F., Prosperini, L., Raz, E., Pace, G., Pantano, P., et al. (2013). Assessing the correlation between grey and white matter damage with motor and cognitive impairment in multiple sclerosis patients. *PLoS ONE*, **8**, e63250.

Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., and Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA*, **302**, 627–637.

Schmidt, D., and Schachter, S. C. (2014). Drug treatment of epilepsy in adults. *BMJ*, **348**, 130–136.

Schneider, J. A., Arvanitakis, Z., Bang, W., and Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*, **69**, 2197–2204.

Schoonheim, M. M., Meijer, K. A., and Geurts, J. J. (2015). Network collapse and cognitive impairment in multiple sclerosis. *Frontiers in Neurology*, **6**.

Schretlen, D. J., and Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry*, **15**, 341–349.

Schuff, N., Woerner, N., Boreat, L., Kornfield, T., Shaw, L. M., Trojanowski, J. Q., et

al. (2009). MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*, **132**, 1067–1077.

Schwarz, A. (2009a, October 3). Congress to hold hearings on N.F.L. head injuries. *New York Times*.

Schwarz, A. (2009b, September 30). Dementia risk seen in players in N.F.L. study. *New York Times*.

Sharma, R., Tripathi, M., D'Souza, M., Jaimini, A., Varshney, R., Panwar, P., ... and Singh, D. (2011). Spectrum of neurocognitive dysfunction in Indian population on FDG PET/CT imaging. *Indian Journal of Nuclear Medicine: IJNM*, **26**(2), 67.

Sharp, D. J., Scott, G., and Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews. Neurology*, **10**, 156.

Sherman, E., Wiebe, S., Fay-McClymont, T. B., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., Jetté, N., et al. (2011). Neuropsychological outcomes after epilepsy surgery: Systematic review and pooled estimates. *Epilepsia*, **52**, 857–869.

Siebert, R. J., and Abernethy, D. A. (2005). Depression in multiple sclerosis: A review. *Journal of Neurology, Neurosurgery, and Psychiatry*, **76**, 469–475.

Smith, D. H., Johnson, V. E., and Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: Substrates of dementia? *Nature Reviews Neurology*, **9**(4), 211–221.

Snowdon, D. A., Kemper, S. J., Mortimer, J. A., Greiner, L. H., Wekstein, D. R., and Markesbery, W. R. (1996). Linguistic ability in early life and cognitive function and Alzheimer's Disease in late life: Findings from the Nun Study. *JAMA*, **275**, 528–532.

Solomon, A. C., Stout, J. C., Weaver, M., Queller, S., Tomusk, A., Whitlock, K. B., Beristain, X., et al. (2008). Ten-year rate of longitudinal change in neurocognitive and

motor function in prediagnosis Huntington disease. *Movement Disorders*, **23**, 1830–1836.

Sperling, R., Mormino, E., and Johnson, K. (2014). The evolution of preclinical Alzheimer's disease: Implications for prevention trials. *Neuron*, **84**, 608–622.

Spires-Jones, T. L., Stoothoff, W. H., de Calignon, A., Jones, P. B., and Hyman, B. T. (2009). Tau pathophysiology in neurodegeneration: A tangled issue. *Trends in Neurosciences*, **32**, 150–159.

Stafstrom, C. E., and Carmant, L. (2015). Seizures and epilepsy: An overview for neuroscientists. *Cold Spring Harbor Perspectives in Medicine*, **5**, a022426.

Stender, J., Gosseries, O., Bruno, M. A., Charland-Verville, V., Vanhaudenhuyse, A., Demertzi, A., Soddu, A., et al. (2014). Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: A clinical validation study. *The Lancet*, **384**, 514–522.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, **11**, 1006–1012.

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Johnson, S. A., et al. (2011). Neurocognitive signs in prodromal Huntington disease. *Neuropsychology*, **25**, 1–14.

Summers, M. J., and Saunders, N. L. (2012). Neuropsychological measures predict decline to Alzheimer's dementia from mild cognitive impairment. *Neuropsychology*, **26**, 498–508.

Svenningsson, P., Westman, E., Ballard, C., and Aarsland, D. (2012). Cognitive impairment in patients with Parkinson's disease: Diagnosis, biomarkers, and treatment. *The Lancet Neurology*, **11**, 697–707.

Tate, R., Kennedy, M., Ponsford, J., Douglas, J., Velikonja, D., Bayley, M., and Stergiou-Kita, M. (2014). INCOG recommendations for management of cognition following traumatic brain injury, part III: Executive function and self-awareness. *Journal of Head Trauma Rehabilitation*, **29**, 338–352.

Teasdale, G., and Jennett, B. (1974). Assessment of coma and impaired consciousness: A practical scale. *Lancet*, **2**, 81–84.

Teasdale, G., Maas, A., Lecky, F., Manley, G., Stocchetti, N., and Murray, G. (2014). The Glasgow Coma Scale at 40 years: Standing the test of time. *The Lancet Neurology*, **13**, 844–854.

Trapp, B. D., and Nave, K. A. (2008). Multiple sclerosis: An immune or neurodegenerative disorder? *Annual Review of Neuroscience*, **31**, 247–269.

Udekwu, P., Kromhout-Schiro, S., Vaslef, S., Baker, C., and Oller, D. (2004). Glasgow Coma Scale score, mortality, and functional outcome in head-injured patients. *Journal of Trauma Injury, Infection, and Critical Care*, **56**, 1084–1089.

Unschuld, P. G., Joel, S. E., Liu, X., Shanahan, M., Margolis, R. L., Biglan, K. M., Pekar, J. J., et al. (2012). Impaired cortico-striatal functional connectivity in prodromal Huntington's disease. *Neuroscience Letters*, **514**, 204–209.

van Donkelaar, P., Langan, J., Rodriguez, E., Drew, A., Halterman, C., Osternig, L. R., and Chou, L.-S. (2005). Attentional deficits in concussion. *Brain Injury*, **19**, 1031–1039.

Velikonja, D., Tate, R., Ponsford, J., McIntyre, A., Janzen, S., and Bayley, M. (2014). INCOG recommendations for management of cognition following traumatic brain injury, part V: Memory. *Journal of Head Trauma Rehabilitation*, **29**, 369–386.

Venkat, P., Chopp, M., and Chen, J. (2015). Models and mechanisms of vascular dementia. *Experimental Neurology*, **272**, 97–108.

Verma, M., and Howard, R. J. (2012). Semantic memory and language dysfunction in early Alzheimer's disease: A review. *International Journal of Geriatric Psychiatry*, **27**, 1209–1217.

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., Ames, D., et al. (2013). Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. *The Lancet Neurology*, **12**, 357–367.

Wahlin, T.-B. R., Lundin, A., and Dear, K. (2007). Early cognitive deficits in Swedish gene carriers of Huntington's disease. *Neuropsychology*, **21**, 31–44.

Warren, J. D., Rohrer, J. D., and Rossor, M. N. (2013). Frontotemporal dementia. *BMJ*, **347**, f4827.

Weil, Z. M., Corrigan, J. D., and Karelina, K. (2016). Alcohol abuse after traumatic brain injury: Experimental and clinical evidence. *Neuroscience and Biobehavioral Reviews*, **62**, 89–99.

Weiner, M. W., Veitch, D. P., Aisen, P. S., Beckett, L. A., Cairns, N. J., Cedarbaum, J., Jagust, W., et al. (2015). Impact of the Alzheimer's disease neuroimaging initiative, 2004 to 2014. *Alzheimer's and Dementia*, **11**, 865–884.

Wingerchuk, D. M., and Carter, J. L. (2014). Multiple sclerosis: Current and emerging disease-modifying therapies and treatment strategies. *Mayo Clinic Proceedings*, **89**, 225–240.

Xiong, Y., Mahmood, A., and Chopp, M. (2013). Animal models of traumatic brain injury. *Nature Reviews Neuroscience*, **14**, 128–142.

Zeman, A. (1997). Persistent vegetative state. *Lancet*, **350**, 795–799.

Zemper, E. D. (2003). Two-year prospective study of relative risk of a second cerebral concussion. *American Journal of Physical Medicine and Rehabilitation*, **82**, 653–659.

Zhang, X., Mormino, E. C., Sun, N., Sperling, R. A., Sabuncu, M. R., Yeo, B. T., Jack, C. R., et al. (2016). Bayesian model reveals latent atrophy factors with dissociable cognitive trajectories in Alzheimer's disease. *Proceedings of the National Academy of Sciences*, **113**, E6535–E6544.

Zhang, Y., Schuff, N., Du, A.-T., Rosen, H. J., Kramer, J. H., Gorno-Tempini, M. L., et al. (2009). White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. *Brain*, **132**, 2579–2592.

Chapter 17

Abe, N. (2011). How the brain shapes deception: An integrated review of the literature. *The Neuroscientist*, **17**(5), 560–574.

Aharoni, E., Vincent, G. M., Harenski, C. L., Calhoun, V. D., Sinnott-Armstrong, W., Gazzaniga, M. S., and Kiehl, K. A. (2013). Neuroprediction of future rearrest. *Proceedings of the National Academy of Sciences*, **110**(15), 6223–6228.

Ali, S. S., Lifshitz, M., and Raz, A. (2014). Empirical neuroenchantment: From reading minds to thinking critically. *Frontiers in Human Neuroscience*, **8**.

Allgaier, J., Dunwoody, S., Brossard, D., Lo, Y. Y., and Peters, H. P. (2013). Medialized science? Neuroscientists' reflections on their role as journalistic sources. *Journalism Practice*, **7**(4), 413–429.

American Medical Association. (2009, July 23). [Amicus curiae brief filed in U.S. Supreme Court in *Graham v. Florida*, 560 U.S. **48** (2010)].

Andrews-Hanna, J. R., Mackiewicz Seghete, K. L., Claus, E. D., Burgess, G. C., Ruzic, L., and Banich, M. T. (2011). Cognitive control in adolescence: Neural underpinnings and relation to self-report behaviors. *PLoS ONE*, **6**(6), e21598.

Ariely, D., and Berns, G. S. (2010). Neuromarketing: The hope and hype of neuroimaging in business. *Nature Reviews Neuroscience*, **11**(4), 284–292.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, **10**(6), 410–422.

Arnsten, A. F., Raskind, M. A., Taylor, F. B., and Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of Stress*, **1**, 89–99.

Bach, S., Richardson, U., Brandeis, D., Martin, E., and Brem, S. (2013). Print-specific multimodal brain activation in kindergarten improves prediction of reading skills in second grade. *Neuroimage*, **82**, 605–615.

Baker, D. A., Ware, J. M., Schweitzer, N. J., and Risko, E. F. (2017). Making sense of research on the neuroimage bias. *Public Understanding of Science*, **26**(2), 251–258.

Beck, D. M. (2010). The appeal of the brain in the popular press. *Perspectives on Psychological Science*, **5**(6), 762–766.

Berker, S. (2009). The normative insignificance of neuroscience. *Philosophy and Public Affairs*, **37**(4), 293–329.

Blair, C., Granger, D. A., Willoughby, M., Mills-Koonce, R., Cox, M., Greenberg, M. T., Fortunato, C. K., et al. (2011). Salivary cortisol mediates effects of poverty and parenting on executive functions in early childhood. *Child Development*, **82**(6), 1970–1984.

Blair, C., and Raver, C. C. (2014). Closing the achievement gap through modification of neurocognitive and neuroendocrine function: Results from a cluster randomized controlled trial of an innovative approach to the education of children in kindergarten. *PLoS ONE*, **9**(11).

Bond, C. F., and DePaulo, B. M. (2006). Accuracy of deception judgments. *Personality and Social Psychology Review*, **10**(3), 214–234.

Borghini, G., Astolfi, L., Vecchiato, G., Mattia, D., and Babiloni, F. (2014). Measuring neurophysiological signals in aircraft pilots and car drivers for the assessment of mental workload, fatigue and drowsiness. *Neuroscience and Biobehavioral Reviews*, **44**, 58–75.

Bradley, R. H., and Corwyn, R. F. (2002). Socioeconomic status and child

development. *Annual Review of Psychology*, **53**(1), 371–399.

Bräuer, J., and Hanus, D. (2012). Fairness in non-human primates? *Social Justice Research*, **25**(3), 256–276.

Brosnan, S. F. (2013). Justice-and fairness-related behaviors in nonhuman primates. *Proceedings of the National Academy of Sciences*, **110**(Suppl. 2), 10416–10423.

Brosnan, S. F., and de Waal, F. B. (2003). Monkeys reject unequal pay. *Nature*, **425**(6955), 297–299.

Brosnan, S. F., and de Waal, F. B. (2014). Evolution of responses to (un) fairness. *Science*, **346**(6207), 1251776.

Bruer, J. T. (1997). Education and the brain: A bridge too far. *Educational Researcher*, **26**, 4–16.

Bruer, J. T. (2008). Building bridges in neuroeducation. In A. M. Battro, K. W. Fischer, and P. J. Léna (eds.), *The educated brain: Essays in neuroeducation*. Cambridge: Cambridge University Press.

Buchen, L. (2012). Arrested development. *Nature*, **484**, 304–306.

Cameron, W., and Chudler, E. (2003). A role for neuroscientists in engaging young minds. *Nature Reviews Neuroscience*, **4**(9), 763–768.

Carew, T. J., and Magsamen, S. H. (2010). Neuroscience and education: An ideal partnership for producing evidence-based solutions to guide 21st century learning. *Neuron*, **67**(5), 685–688.

Caria, A., Sitaram, R., and Birbaumer, N. (2012). Real-Time fMRI: A tool for local brain regulation. *The Neuroscientist*, **18**(5), 487–501.

Cerruti, C., and Schlaug, G. (2009). Anodal transcranial direct current stimulation of the

prefrontal cortex enhances complex verbal associative thought. *Journal of Cognitive Neuroscience*, **21**(10), 1980–1987.

Chancellor, B., and Chatterjee, A. (2011). Brain branding: When neuroscience and commerce collide. *AJOB Neuroscience*, **2**(4), 18–27.

Chapman, H. A., Kim, D. A., Susskind, J. M., and Anderson, A. K. (2009). In bad taste: Evidence for the oral origins of moral disgust. *Science*, **323**(5918), 1222–1226.

Chatterjee, A. (2007). Cosmetic neurology and cosmetic surgery: Parallels, predictions, and challenges. *Cambridge Quarterly of Healthcare Ethics*, **16**(02), 129–137.

Chein, J., Albert, D., O'Brien, L., Uckert, K., and Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental Science*, **14**(2), F1–10.

Cheng, Y., Chen, C., Lin, C. P., Chou, K. H., and Decety, J. (2010). Love hurts: An fMRI study. *Neuroimage*, **51**(2), 923–929.

Christensen, J. F., and Gomila, A. (2012). Moral dilemmas in cognitive neuroscience of moral decision-making: A principled review. *Neuroscience and Biobehavioral Reviews*, **36**(4), 1249–1264.

Christodoulou, J. A., Del Tufo, S. N., Lymberis, J., Saxler, P. K., Ghosh, S. S., Triantafyllou, C., Gabrieli, J. D., et al. (2014). Brain bases of reading fluency in typical reading and impaired fluency in dyslexia. *PLoS ONE*, **9**(7).

Coffman, B. A., Clark, V. P., and Parasuraman, R. (2014). Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *Neuroimage*, **85**, 895–908.

Cohen, O., Druon, S., Lengagne, S., Mendelsohn, A., Malach, R., Kheddar, A., and Friedman, D. (2014). fMRI-based robotic embodiment: Controlling a humanoid robot

by thought using real-time fMRI. *PRESENCE: Teleoperators and Virtual Environments*, **23**(3), 229–241.

Cuthbert, A. S. (2015). Neuroscience and education – an incompatible relationship. *Sociology Compass*, **9**(1), 49–61.

Decety, J., and Cowell, J. M. (2014). The complex relation between morality and empathy. *Trends in Cognitive Sciences*, **18**(7), 337–339.

Decety, J., and Cowell, J. M. (2015). Empathy, justice, and moral behavior. *AJOB Neuroscience*, **6**(3), 3–14.

Decety, J., and Wheatley, T. (2015). *The moral brain: A multidisciplinary perspective*. Cambridge, MA: MIT Press.

deCharms, R. C. (2008). Applications of real-time fMRI. *Nature Reviews Neuroscience*, **9**(9), 720–729.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., Mackey, S. C., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences*, **102**(51), 18626–18631.

Dekker, S., Lee, N. C., Howard-Jones, P., and Jolles, J. (2012). Neuromyths in education: Prevalence and predictors of misconceptions among teachers. *Frontiers in Psychology*, **3**, 429.

Delton, A. W., and Krasnow, M. M. (2015). Adaptationist approaches to moral psychology. In J. Decety and T. Wheatley (eds.), *The moral brain: A multidisciplinary perspective*. Cambridge, MA: MIT Press.

Diamond, A., and Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science*, **333**(6045), 959–964.

Dubinsky, J. M. (2010). Neuroscience education for prekindergarten–12 teachers. *The Journal of Neuroscience*, **30**(24), 8057–8060.

Elliott, J. G., and Gibbs, S. (2008). Does dyslexia exist? *Journal of Philosophy of Education*, **42**(3-4), 475–491.

Eriksson, K. (2012). The nonsense math effect. *Judgment and Decision Making*, **7**, 746–749.

Farah, M. J., and Hook, C. J. (2013). The seductive allure of “seductive allure.” *Perspectives on Psychological Science*, **8**(1), 88–90.

Farah, M. J., Hutchinson, J. B., Phelps, E. A., and Wagner, A. D. (2014). Functional MRI-based lie detection: Scientific and societal challenges. *Nature Reviews Neuroscience*, **15**(2), 123–131.

Farwell, L. A., and Donchin, E. (1991). The truth will out: Interrogative polygraphy (“lie detection”) with event-related brain potentials. *Psychophysiology*, **28**(5), 531–547.

Farwell, L. A., Richardson, D. C., Richardson, G. M., and Furedy, J. J. (2014). Brain fingerprinting classification concealed information test detects US Navy military medical information with P300. *Frontiers in Neuroscience*, **8**.

Fernald, A., Marchman, V. A., and Weisleder, A. (2013). SES differences in language processing skill and vocabulary are evident at 18 months. *Developmental Science*, **16**(2), 234–248.

Fernandez-Duque, D., Evans, J., Christian, C., and Hodges, S. D. (2015). Superfluous neuroscience information makes explanations of psychological phenomena more appealing. *Journal of Cognitive Neuroscience*, **27**(5), 926–944.

Fitzakerley, J. L., Michlin, M. L., Paton, J., and Dubinsky, J. M. (2013).

Neuroscientists' classroom visits positively impact student attitudes. *PLoS ONE*, **8**(12).

Geraci, A., and Surian, L. (2011). The developmental roots of fairness: Infants' reactions to equal and unequal distributions of resources. *Developmental Science*, **14**(5), 1012–1020.

Goswami, U. (2008). Principles of learning, implications for teaching: A cognitive neuroscience perspective. *Journal of Philosophy of Education*, **42**(3–4), 381–399.

Graham v. Florida, 560 U.S. 48 (2010).

Greene, E., and Cahill, B. S. (2012). Effects of neuroimaging evidence on mock juror decision making. *Behavioral Sciences and the Law*, **30**(3), 280–296.

Greene, J. D. (2014). Beyond point-and-shoot morality: Why cognitive (neuro)science matters for ethics. *Ethics*, **124**(4), 695–726.

Greene, J. D. (2015). The cognitive neuroscience of moral judgment and decision-making. In J. Decety and T. Wheatley (eds.), *The moral brain: A multidisciplinary perspective*. Cambridge, MA: MIT Press.

Greene, J. D., Nystrom, L. E., Engell, A. D., Darley, J. M., and Cohen, J. D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, **44**(2), 389–400.

Greene, J. D., Sommerville, R. B., Nystrom, L. E., Darley, J. M., and Cohen, J. D. (2001). An fMRI investigation of emotional engagement in moral judgment. *Science*, **293**(5537), 2105–2108.

Grosbras, M.-H., Jansen, M., Leonard, G., McIntosh, A., Osswald, K., Poulsen, C., et al. (2007). Neural mechanisms of resistance to peer influence in early adolescence. *Journal of Neuroscience*, **27**(30), 8040–8045.

Gruber, D., and Dickerson, J. A. (2012). Persuasive images in popular science: Testing judgments of scientific reasoning and credibility. *Public Understanding of Science*, **21**(8), 938–948.

Hackman, D. A., Farah, M. J., and Meaney, M. J. (2010). Socioeconomic status and the brain: Mechanistic insights from human and animal research. *Nature Reviews Neuroscience*, **11**(9), 651–659.

Haidt, J. (2001). The emotional dog and its rational tail: A social intuitionist approach to moral judgment. *Psychological Review*, **108**(4), 814–834.

Hair, N. L., Hanson, J. L., Wolfe, B. L., and Pollak, S. D. (2015). Association of child poverty, brain development, and academic achievement. *JAMA Pediatrics*, **169**(9), 822–829.

Hamilton, R., Messing, S., and Chatterjee, A. (2011). Rethinking the thinking cap: Ethics of neural enhancement using noninvasive brain stimulation. *Neurology*, **76**(2), 187–193.

Hare, T. A., Camerer, C. F., and Rangel, A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. *Science*, **324**(5927), 646–648.

Hart, B., and Risley, T. R. (1995). Meaningful differences in the everyday experience of young American children. Baltimore, MD: Paul H. Brookes Publishing.

Herculano-Houzel, S. (2002). Do you know your brain? A survey on public neuroscience literacy at the closing of the decade of the brain. *The Neuroscientist*, **8**(2), 98–110.

Herculano-Houzel, S. (2003). What does the public want to know about the brain? *Nature Neuroscience*, **6**(4), 325–325.

Hoef, F., McCandliss, B. D., Black, J. M., Gantman, A., Zakerani, N., Hulme, C., Gabrieli, J. D., et al. (2011). Neural systems predicting long-term outcome in dyslexia.

Proceedings of the National Academy of Sciences, **108**(1), 361–366.

Hoef, F., Ueno, T., Reiss, A. L., Meyler, A., Whitfield-Gabrieli, S., Glover, G. H., Just, M. A., et al. (2007). Prediction of children's reading skills using behavioral, functional, and structural neuroimaging measures. *Behavioral Neuroscience*, **121**(3), 602–613.

Hoff, E. (2003). The specificity of environmental influence: Socioeconomic status affects early vocabulary development via maternal speech. *Child Development*, **74**(5), 1368–1378.

Hoff, E. (2013). Interpreting the early language trajectories of children from low-SES and language minority homes: Implications for closing achievement gaps. *Developmental Psychology*, **49**(1), 4–14.

Hook, C. J., and Farah, M. J. (2013a). Look again: effects of brain images and mind-brain dualism on lay evaluations of research. *Journal of Cognitive Neuroscience*, **25**(9), 1397–1405.

Hook, C. J., and Farah, M. J. (2013b). Neuroscience for educators: What are they seeking, and what are they finding? *Neuroethics*, **6**(2), 331–341.

Howard-Jones, P. A. (2014). Neuroscience and education: Myths and messages. *Nature Reviews Neuroscience*, **15**(12), 817–824.

Huang, J. Y., and Kosal, M. E. (2008). The security impact of the neurosciences. *Bulletin of the Atomic Scientists*.

Husain, M., and Mehta, M. A. (2011). Cognitive enhancement by drugs in health and disease. *Trends in Cognitive Sciences*, **15**(1), 28–36.

Hutcherson, C. A., Montaser-Kouhsari, L., Woodward, J., and Rangel, A. (2015). Emotional and utilitarian appraisals of moral dilemmas are encoded in separate areas and integrated in ventromedial prefrontal cortex. *Journal of Neuroscience*, **35**(36),

12593–12605.

Huttenlocher, J., Waterfall, H., Vasilyeva, M., Vevea, J., and Hedges, L. V. (2010). Sources of variability in children's language growth. *Cognitive Psychology*, **61**(4), 343–365.

Illes, J., Moser, M. A., McCormick, J. B., Racine, E., Blakeslee, S., Caplan, A., Nicholson, C., et al. (2010). Neurotalk: Improving the communication of neuroscience research. *Nature Reviews Neuroscience*, **11**(1), 61–69.

Javor, A., Koller, M., Lee, N., Chamberlain, L., and Ransmayr, G. (2013). Neuromarketing and consumer neuroscience: Contributions to neurology. *BMC Neurology*, **13**(1), 13.

Jednoróg, K., Altarelli, I., Monzalvo, K., Fluss, J., Dubois, J., Billard, C., Ramus, F., et al. (2012). The influence of socioeconomic status on children's brain structure. *PLoS ONE*, **7**(8), e42486.

Jiang, W., Liu, H., Liao, J., Ma, X., Rong, P., Tang, Y., and Wang, W. (2013). A functional MRI study of deception among offenders with antisocial personality disorders. *Neuroscience*, **244**, 90–98.

Jones, O. D., Bonnie, R. J., Casey, B. J., Davis, A., Faigman, D. L., Hoffman, M., et al. (2014). Law and neuroscience: Recommendations submitted to the President's Bioethics Commission. *Journal of Law and the Biosciences*, **1**(2), 224–236.

Kable, J. W., and Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, **10**(12), 1625–1633.

Keehner, M., Mayberry, L., and Fischer, M. H. (2011). Different clues from different views: The role of image format in public perceptions of neuroimaging results. *Psychonomic Bulletin and Review*, **18**(2), 422–428.

Kishiyama, M. M., Boyce, W. T., Jimenez, A. M., Perry, L. M., and Knight, R. T. (2009). Socioeconomic disparities affect prefrontal function in children. *Journal of Cognitive Neuroscience*, **21**(6), 1106–1115.

Kovelman, I., Norton, E. S., Christodoulou, J. A., Gaab, N., Lieberman, D. A., Triantafyllou, C., Gabrieli, J. D., et al. (2012). Brain basis of phonological awareness for spoken language in children and its disruption in dyslexia. *Cerebral Cortex*, **22**(4), 754–764.

Kozel, F. A., Johnson, K. A., Grenesko, E. L., Laken, S. J., Kose, S., Lu, X., George, M. S., et al. (2009). Functional MRI detection of deception after committing a mock sabotage crime. *Journal of Forensic Sciences*, **54**(1), 220–231.

Kozel, F. A., Johnson, K. A., Mu, Q., Grenesko, E. L., Laken, S. J., and George, M. S. (2005). Detecting deception using functional magnetic resonance imaging. *Biological Psychiatry*, **58**(8), 605–613.

Krafnick, A. J., Flowers, D. L., Luetje, M. M., Napoliello, E. M., and Eden, G. F. (2014). An investigation into the origin of anatomical differences in dyslexia. *Journal of Neuroscience*, **34**(3), 901–908.

Langford, D. J., Tuttle, A. H., Brown, K., Deschenes, S., Fischer, D. B., Mutso, A., Sternberg, W. F., et al. (2010). Social approach to pain in laboratory mice. *Social Neuroscience*, **5**(2), 163–170.

Langleben, D. D., and Moriarty, J. C. (2013). Using brain imaging for lie detection: Where science, law, and policy collide. *Psychology, Public Policy, and Law*, **19**(2), 222–234.

Langleben, D. D., Schroeder, L., Maldjian, J. A., Gur, R. C., McDonald, S., Ragland, J. D., Childress, A. R., et al. (2002). Brain activity during simulated deception: An event-related functional magnetic resonance study. *Neuroimage*, **15**(3), 727–732.

Lawson, G. M., Duda, J. T., Avants, B. B., Wu, J., and Farah, M. J. (2013). Associations between children's socioeconomic status and prefrontal cortical thickness. *Developmental Science*, **16**(5), 641–652.

Lebedev, M. A., Tate, A. J., Hanson, T. L., Li, Z., O'Doherty, J. E., Winans, J. A., Fuller, A. M., et al. (2011). Future developments in brain-machine interface research. *Clinics*, **66**, 25–32.

Liberzon, I., Ma, S. T., Okada, G., Ho, S. S., Swain, J. E., and Evans, G. W. (2015). Childhood poverty and recruitment of adult emotion regulatory neurocircuitry. *Social Cognitive and Affective Neuroscience*, e-publication in advance of print.

Lindell, A. K., and Kidd, E. (2011). Why right-brain teaching is half-witted: A critique of the misapplication of neuroscience to education. *Mind, Brain, and Education*, **5**(3), 121–127.

Lipina, S. J., and Posner, M. I. (2012). The impact of poverty on the development of brain networks. *Frontiers in Human Neuroscience*, **6**.

Liptak, A. (2010, May 17). Justices limit life sentences for juveniles. *New York Times*.

Liston, C., McEwen, B. S., and Casey, B. J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences*, **106**(3), 912–917.

Madsen, K. S., Baaré, W. F. C., Vestergaard, M., Skimminge, A., Ejersbo, L. R., Ramsøy, T. Z., et al. (2010). Response inhibition is associated with white matter microstructure in children. *Neuropsychologia*, **48**(4), 854–862.

Maurer, U., Bucher, K., Brem, S., Benz, R., Kranz, F., Schulz, E., Brandeis, D., et al. (2009). Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biological Psychiatry*, **66**(4), 341–348.

McCabe, D. P., and Castel, A. D. (2008). Seeing is believing: The effect of brain images on judgments of scientific reasoning. *Cognition*, **107**(1), 343–352.

McEwen, B. S., and Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences*, **1186**, 190–222.

Metzinger, T., and Hildt, E. (2011). Cognitive enhancement. In J. Illes and B. J. Sahakian (eds.), *The Oxford handbook of neuroethics*. Oxford: Oxford University Press.

Meynen, G. (2013). A neurolaw perspective on psychiatric assessments of criminal responsibility: Decision-making, mental disorder, and the brain. *International Journal of Law and Psychiatry*, **36**(2), 93–99.

Michael, R. B., Newman, E. J., Vuorre, M., Cumming, G., and Garry, M. (2013). On the (non) persuasive power of a brain image. *Psychonomic Bulletin and Review*, **20**(4), 720–725.

Miller v. Alabama, 567 U.S. ____ (2012).

Miranda, R. A., Casebeer, W. D., Hein, A. M., Judy, J. W., Krotkov, E. P., Laabs, T. L., Weber, D. J., et al. (2015). DARPA-funded efforts in the development of novel brain-computer interface technologies. *Journal of Neuroscience Methods*, **244**, 52–67.

Mol, S. E., and Bus, A. G. (2011). To read or not to read: A meta-analysis of print exposure from infancy to early adulthood. *Psychological Bulletin*, **137**(2), 267–296.

Molenberghs, P., Gapp, J., Wang, B., Louis, W. R., and Decety, J. (2016). Increased moral sensitivity for outgroup perpetrators harming ingroup members. *Cerebral Cortex*, **26**(1), 225–233.

Molfese, D. L., Molfese, V. J., and Molfese, P. J. (2007). Relation between early measures of brain responses to language performance on language and language-related

tasks. In D. Coch, G. Dawson, and K. W. Fischer (eds.), *Human behavior, learning, and the developing brain: Atypical development* (pp. 191–211). New York: Guilford Press.

Morein-Zamir, S., and Sahakian, B. J. (2011). Pharmaceutical cognitive enhancement. In J. Illes and B. J. Sahakian (eds.), *The Oxford handbook of neuroethics*. Oxford: Oxford University Press.

Myers, C. A., Vandermosten, M., Farris, E. A., Hancock, R., Gimenez, P., Black, J. M., Hulme, C., et al. (2014). White matter morphometric changes uniquely predict children's reading acquisition. *Psychological Science*, **25**(10), 1870–1883.

Neville, H., Pakulak, E., and Stevens, C. (2015). Family-based training to improve cognitive outcomes for children from lower socioeconomic status backgrounds: Emerging themes and challenges. *Current Opinion in Behavioral Sciences*, **4**, 166–170.

Neville, H. J., Stevens, C., Pakulak, E., Bell, T. A., Fanning, J., Klein, S., and Isbell, E. (2013). Family-based training program improves brain function, cognition, and behavior in lower socioeconomic status preschoolers. *Proceedings of the National Academy of Sciences*, **110**(29), 12138–12143.

Nickerson, R. S. (1998). Confirmation bias: A ubiquitous phenomenon in many guises. *Review of General Psychology*, **2**(2), 172–220.

Nicolelis, M. A., and Lebedev, M. A. (2009). Principles of neural ensemble physiology underlying the operation of brain-machine interfaces. *Nature Reviews Neuroscience*, **10**(7), 530–540.

Noble, K. G. (2014). Rich man, poor man: Socioeconomic adversity and brain development. In *Cerebrum: The Dana forum on brain science* (Vol. **2014**). New York: Dana Foundation.

Noble, K. G., Engelhardt, L. E., Brito, N. H., Mack, L. J., Nail, E. J., Angal, J., Elliott, A. J., et al. (2015). Socioeconomic disparities in neurocognitive development in the

first two years of life. *Developmental Psychobiology*, **57**(5), 535–551.

Noble, K. G., Houston, S. M., Brito, N. H., Bartsch, H., Kan, E., Kuperman, J. M., Schork, N. J., et al. (2015). Family income, parental education and brain structure in children and adolescents. *Nature Neuroscience*, **18**(5), 773–778.

Noble, K. G., McCandliss, B. D., and Farah, M. J. (2007). Socioeconomic gradients predict individual differences in neurocognitive abilities. *Developmental Science*, **10**(4), 464–480.

Norton, E. S., Beach, S. D., and Gabrieli, J. D. (2015). Neurobiology of dyslexia. *Current Opinion in Neurobiology*, **30**, 73–78.

O’Connell, G., de Wilde, J., Haley, J., Shuler, K., Schafer, B., Sandercock, P., and Wardlaw, J. M. (2011). The brain, the science and the media. *EMBO Reports*, **12**(7), 630–636.

O’Connor, C., and Joffe, H. (2013). How has neuroscience affected lay understandings of personhood? A review of the evidence. *Public Understanding of Science*, **22**(3), 254–268.

Papp, K. V., Walsh, S. J., and Snyder, P. J. (2009). Immediate and delayed effects of cognitive interventions in healthy elderly: A review of current literature and future directions. *Alzheimer’s and Dementia*, **5**(1), 50–60.

Pascual-Leone, A., Fregni, F., Steven-Wheeler, M. S., and Forrow, L. (2011). Non-invasive brain stimulation as a therapeutic and investigative tool. In J. Illes and B. J. Sahakian (eds.), *The Oxford handbook of neuroethics*. Oxford: Oxford University Press.

Pasquinelli, E. (2012). Neuromyths: Why do they exist and persist? *Mind, Brain, and Education*, **6**(2), 89–96.

Peterson, R. L., and Pennington, B. F. (2012). Developmental dyslexia. *The Lancet*,

379(9830), 1997–2007.

Pickering, S. J., and Howard-Jones, P. (2007). Educators' views on the role of neuroscience in education: Findings from a study of UK and international perspectives. *Mind, Brain, and Education*, **1**(3), 109–113.

Plassmann, H., O'Doherty, J., and Rangel, A. (2007). Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *Journal of Neuroscience*, **27**(37), 9984–9988.

Plassmann, H., O'Doherty, J., Shiv, B., and Rangel, A. (2008). Marketing actions can modulate neural representations of experienced pleasantness. *Proceedings of the National Academy of Sciences*, **105**(3), 1050–1054.

Plassmann, H., Ramsøy, T. Z., and Milosavljevic, M. (2012). Branding the brain: A critical review and outlook. *Journal of Consumer Psychology*, **22**(1), 18–36.

Prétôt, L., and Brosnan, S. (2015). The evolution of morality: A comparative approach. In J. Decety and T. Wheatley (eds.), *The moral brain: A multidisciplinary perspective*. Cambridge, MA: MIT Press.

Racine, E., Bar-Ilan, O., and Illes, J. (2006). Brain imaging: A decade of coverage in the print media. *Science Communication*, **28**(1), 122–143.

Racine, E., and Forlini, C. (2010). Cognitive enhancement, lifestyle choice or misuse of prescription drugs? *Neuroethics*, **3**(1), 1–4.

Racine, E., Waldman, S., Rosenberg, J., and Illes, J. (2010). Contemporary neuroscience in the media. *Social Science and Medicine*, **71**(4), 725–733.

Ragan, C. I., Bard, I., and Singh, I. (2013). What should we do about student use of cognitive enhancers? An analysis of current evidence. *Neuropharmacology*, **64**, 588–595.

Raizada, R. D., and Kishiyama, M. M. (2010). Effects of socioeconomic status on brain development, and how cognitive neuroscience may contribute to levelling the playing field. *Frontiers in Human Neuroscience*, **4**(3).

Raschle, N. M., Zuk, J., and Gaab, N. (2012). Functional characteristics of developmental dyslexia in left-hemispheric posterior brain regions predate reading onset. *Proceedings of the National Academy of Sciences*, **109**(6), 2156–2161.

Reimann, M., Schilke, O., Weber, B., Neuhaus, C., and Zaichkowsky, J. (2011). Functional magnetic resonance imaging in consumer research: A review and application. *Psychology and Marketing*, **28**(6), 608–637.

Rolls, E. T., McCabe, C., and Redoute, J. (2008). Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. *Cerebral Cortex*, **18**(3), 652–663.

Roper v. Simmons, 543 U.S. 551 (2005).

Rosenfeld, J. P. (2005). Brain fingerprinting: A critical analysis. *Scientific Review of Mental Health Practice*, **4**(1), 20–37.

Royal Society. (2012). *Brain waves 3: Neuroscience, conflict, and security*. London: Royal Society.

Rusconi, E., and Mitchener-Nissen, T. (2013). Prospects of functional magnetic resonance imaging as lie detector. *Frontiers in Human Neuroscience*, **7**.

Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., Gabrieli, J. D., et al. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *Journal of Neuroscience*, **33**(33), 13251–13258.

Scharnowski, F., Hutton, C., Josephs, O., Weiskopf, N., and Rees, G. (2012). Improving

visual perception through neurofeedback. *Journal of Neuroscience*, **32**(49), 17830–17841.

Schauer, F. (2010). Neuroscience, lie-detection, and the law: Contrary to the prevailing view, the suitability of brain-based lie-detection for courtroom or forensic use should be determined according to legal and not scientific standards. *Trends in Cognitive Sciences*, **14**(3), 101–103.

Schmiedek, F., Lövdén, M., and Lindenberger, U. (2010). Hundred days of cognitive training enhance broad cognitive abilities in adulthood: Findings from the COGITO study. *Frontiers in Aging Neuroscience*, **2**, 27.

Schweitzer, N. J., Baker, D. A., and Risko, E. F. (2013). Fooled by the brain: Re-examining the influence of neuroimages. *Cognition*, **129**(3), 501–511.

Schweitzer, N. J., Saks, M. J., Murphy, E. R., Roskies, A. L., Sinnott-Armstrong, W., and Gaudet, L. M. (2011). Neuroimages as evidence in a mens rea defense: No impact. *Psychology, Public Policy, and Law*, **17**(3), 357–393.

Scurich, N., and Shniderman, A. B. (2014). The selective allure of neuroscientific explanations. *PLoS ONE*, **9**(9).

Shenhav, A., and Greene, J. D. (2014). Integrative moral judgment: Dissociating the roles of the amygdala and ventromedial prefrontal cortex. *Journal of Neuroscience*, **34**(13), 4741–4749.

Sheridan, M. A., Sarsour, K., Jutte, D., D'Esposito, M., and Boyce, W. T. (2012). The impact of social disparity on prefrontal function in childhood. *PLoS ONE*, **7**(4), e35744.

Sigman, M., Peña, M., Goldin, A. P., and Ribeiro, S. (2014). Neuroscience and education: Prime time to build the bridge. *Nature Neuroscience*, **17**(4), 497–502.

Sirin, S. R. (2005). Socioeconomic status and academic achievement: A meta-analytic review of research. *Review of Educational Research*, **75**(3), 417–453.

Sloane, S., Baillargeon, R., and Premack, D. (2012). Do infants have a sense of fairness? *Psychological Science*, **23**(2), 196–204.

Smith, M. E., and Farah, M. J. (2011). Are prescription stimulants “smart pills”? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin*, **137**(5), 717–741.

Sperduti, A., Crivellaro, F., Rossi, P. F., and Bondioli, L. (2012). “Do octopuses have a brain?” Knowledge, perceptions and attitudes towards neuroscience at school. *PloS ONE*, **7**(10), e47943.

Steinberg, L. (2009). Adolescent development and juvenile justice. *Annual Review of Clinical Psychology*, **5**, 459–485.

Steinberg, L., Cauffman, E., Woolard, J., Graham, S., and Banich, M. (2009). Are adolescents less mature than adults? Minors’ access to abortion, the juvenile death penalty, and the alleged APA “flip-flop.” *American Psychologist*, **64**(7), 583–594.

Stevens, C., Lauinger, B., and Neville, H. (2009). Differences in the neural mechanisms of selective attention in children from different socioeconomic backgrounds: An event-related brain potential study. *Developmental Science*, **12**, 634–646.

Tennison, M. N., and Moreno, J. D. (2012). Neuroscience, ethics, and national security: The state of the art. *PLoS Biology*, **10**, e1001289.

Thakor, N. V. (2013). Translating the brain–machine interface. *Science Translational Medicine*, **5**(210), 210ps17.

Tracey, I., and Flower, R. (2014). The warrior in the machine: Neuroscience goes to

war. *Nature Reviews Neuroscience*, **16**(3), 184–184.

van Atteveldt, N. M., van Aalderen-Smeets, S. I., Jacobi, C., and Ruigrok, N. (2014). Media reporting of neuroscience depends on timing, topic and newspaper type. *PLoS ONE*, **9**(8).

van Wolkenten, M., Brosnan, S. F., and de Waal, F. B. (2007). Inequity responses of monkeys modified by effort. *Proceedings of the National Academy of Sciences*, **104**(47), 18854–18859.

Wander, J. D., and Rao, R. P. (2014). Brain–computer interfaces: A powerful tool for scientific inquiry. *Current Opinion in Neurobiology*, **25**, 70–75.

Wardlaw, J. M., O’Connell, G., Shuler, K., DeWilde, J., Haley, J., Escobar, O., Schafer, B., et al. (2011). “Can it read my mind?” What do the public and experts think of the current (mis) uses of neuroimaging? *PloS ONE*, **6**(10), e25829–e25829.

Weisberg, D. S., Keil, F. C., Goodstein, J., Rawson, E., and Gray, J. R. (2008). The seductive allure of neuroscience explanations. *Journal of Cognitive Neuroscience*, **20**(3), 470–477.

Weisberg, D. S., Taylor, J. C., and Hopkins, E. J. (2015). Deconstructing the seductive allure of neuroscience explanations. *Judgment and Decision Making*, **10**(5), 429–441.

Yoder, K. J., and Decety, J. (2014a). Spatiotemporal neural dynamics of moral judgment: A high-density ERP study. *Neuropsychologia*, **60**, 39–45.

Yoder, K. J., and Decety, J. (2014b). The good, the bad, and the just: Justice sensitivity predicts neural response during moral evaluation of actions performed by others. *Journal of Neuroscience*, **34**(12), 4161–4166.

Index

abstract and conceptual thinking, [354–356](#)
acetylcholine (Ach), [20–21](#), [298](#)
across-hemisphere processing, [61–62](#)
action potential, [15–17](#)
action tremor, [105](#)
activating-orienting model, [57](#)
adaptation method, [179–180](#)
agnosia, landmark, [217](#)
agnosias, auditory, [193](#), See also [object recognition](#)
agnosias, tactile, [193](#), See also [object recognition](#)
agnosias, visual. See also [ventral stream](#), [object recognition](#)
 apperceptive/associative, [171–174](#)
 definition of, [36](#), [171](#)
 prosopagnosia, [174–175](#)
agraphia, [35](#), [242–243](#), [244](#)
akinesia, [127](#)
alexia, [35](#), [242–243](#)
Ali, Muhammad, [101](#)
allocentric reference frames, [203–204](#)
Alzheimer's disease. See also [dementia](#)
 diagnosis, [500–502](#)
 effectiveness of ginkgo, [24–25](#)
 genetic bases and risk factors, [506–507](#)
 impact of head injury, [496](#)

- neurophysiological bases, [503–506](#)
- neuropsychological profile, [502–503](#)
- role of acetylcholine, [21](#)
- similarities to vascular disease, [513–514](#)
- treatment and prevention, [507–508](#)

American Sign Language (ASL), [238–240](#)

amino acids, [19](#)

amnesia

- as a pathway to understanding memory systems, [257–258](#)
- damage to the hippocampus and, [259](#)
- impact on skill learning, [264–267](#)
- impact on working memory, [263–264](#)
- temporal phases of, [261–263](#)

amygdala

- influence in anxiety disorders, [445–446](#)
- interface between memory and emotion, [275–277](#)
- neural network of, [373–374](#)
- role in emotional learning, [371–373](#)
- role in interpretation of facial expressions, [386](#)

amygdalar complex, [371](#)

amyloid plaques, [504](#)

analogical reasoning, [354–356](#)

anhedonia, [437](#)

anisometry hypothesis, [324](#)

anterior cingulate cortex. See also [cingulate cortex](#)

- integration of emotion and action, [379–381](#)
- motor control, [118–119](#)
- response selection, [307](#)

anterograde disorientation, [217](#)

anxiety disorders

- influence of cortical regions, [446–449](#)

influence of the amygdala and hippocampus, [445–446](#)
symptoms and features, [444–445](#)
anxious apprehension, [444](#)
anxious arousal, [444](#)
apathy, [337–339](#)
aphasia
 Broca's, [224](#), [225–226](#)
 impact of lesion location, [227–228](#)
 phonology issues, [229–230](#)
 semantics issues, [231–238](#)
 syntax issues, [230–231](#)
 Wernicke's, [226–227](#)
approach-withdrawal model, [391](#)
apraxia
 brain damage location, [132](#), [134](#)
 classification models, [132–134](#)
 other forms of, [134](#)
aprosodia, [389](#)
arousal/alertness, [298–300](#)
ascending reticular activating system (ARAS), [298–300](#)
Asch, Solomon, [397](#)
Asperger syndrome, [411](#)
athetosis, [110](#)
attention. See also [attention-deficit hyperactivity disorder](#), [attentional control](#),
 [attention, selective](#)
 arousal/alertness, [297](#), [298–300](#)
 as an information biasing mechanism, [311–313](#)
 divided, [313–315](#)
 impact of head injury, [496](#)
 influence of consciousness, [329–330](#)

lapses of, [317–319](#)

object- and space-based, [326–327](#)

processing of unattended stimuli, [328–329](#)

vigilance, [297](#), [300](#)

attention, selective

definition of, [298](#)

parietal lobe, [303–306](#)

superior colliculus, [302–303](#)

thalamus in, [303](#)

time course of, [301–302](#)

attentional control

hemispheric differences in, [327–328](#)

network models of, [315–319](#)

role of prefrontal cortex in, [306–307](#)

sites of, [309–311](#)

sources of, [308–309](#)

attentional functions

impact of acetylcholine depletion on, [21](#)

impact of noradrenaline on, [22](#)

role of parietal region in, [69–70](#)

attentional processing and hemineglect, [322](#)

attentional set, [339–341](#)

attention-deficit hyperactivity disorder, [474–476](#), See also [attention](#)

auditory cortex, [30–32](#), [36](#), [161–163](#)

auditory processing

auditory pathways, [156–159](#)

auditory-visual interactions, [163–164](#)

brainstem computation of spatial location, [159–161](#)

computational problems, [155–156](#)

organization of auditory cortex, [161–163](#)

auditory-visual interactions, [163–164](#)

autism

causes of, [472–474](#)

social cognition impairment, [411–413](#)

autism spectrum disorder, [411](#)

axon, [4](#)

basal ganglia. See also [nervous system](#)

facial expressions, [387](#)

impact on skill learning, [273–275](#)

motor control, [12–14](#), [107–110](#)

behavior assessment

role of cognitive theories, [71](#)

techniques, [71–74](#)

Berger, Hans, [49](#)

biased competition, [311–313](#)

bilingualism, [241–242](#)

binocular disparity, [147](#), [202](#)

binocular imagery, [149–150](#)

binocular integration, [146–148](#)

blindsight, [137](#), [152–153](#)

blood oxygen level dependent (BOLD) signal, [79–80](#)

blood-brain barrier, [4](#)

body image recognition, [190](#)

body movement. See [motion perception](#)

body temperature regulation, [11](#)

Bogen, Joseph, [53–54](#)

bottom-up attentional selection, [300](#), [312–313](#)

bradykinesia, [127](#)

bradyphrenia, [509](#)

brain activity

functional magnetic resonance imaging (fMRI), [79–85](#)

limitations of PET, [65](#)

regions involved in musical activities, [249–250](#)

techniques to modulate, [90–92](#)

the use of EEGs to record, [49–51](#)

brain anatomy, [74–77](#)

brain conductivity

and white matter, [36–37](#)

role of corpus callosum, [53–56](#)

brain connectivity, [84–85](#), [460–461](#)

brain damage recovery

adults, [482–483](#)

children, [483–484](#)

neurophysiological responses, [479–480](#)

regional mechanisms for, [480–482](#)

brain development. See also [brain development, childhood](#), [brain development, adult](#),
[brain development, adolescence](#)

developmental disorders, [468–469](#)

impact of socio-economic status on, [528–530](#)

infections and toxins, [469–470](#)

brain development, adolescence. See also [brain development](#)

impact of environment on, [464–468](#)

legal culpability, [531–532](#)

neural, cognitive and emotional features, [461–464](#)

brain development, adult, [476–479](#), See also [brain development](#)

brain development, childhood. See also [brain development](#)

in utero, [457](#)

neural and cognitive development, [461](#)

physiological changes, [457–461](#)

brain electrical activity measurement methods

electroencephalography (EEG), [85–86](#)

event-related potentials, [86–89](#)

magnetoencephalography (MEG), [88–89](#)

brain fissures, [13–14](#)

brain function

age-related changes, [485–489](#)

impact of lesion method on comprehension of, [42–44](#), [45–46](#)

integration of information between the hemispheres, [60–62](#)

therapies to slow age-related decline, [488–489](#)

brain hemispheres

communication of information between, [60–62](#)

functions of, [53–56](#)

hemineglect and imbalance between, [324–325](#)

lateralization of function, [56–57](#)

modes of information processing, [57–59](#)

specialized functions of, [54–56](#)

brain imaging technology

computerized axial tomography (CAT), [62–64](#)

face recognition, [187–189](#)

lie detection, [532–533](#)

magnetic resonance imaging (MRI), [65–66](#)

positron emission tomography (PET), [62–65](#)

brain mapping, [48–51](#)

brain metabolic activity measurement methods

blood oxygen level dependent (BOLD) signal, [79–80](#)

functional brain connectivity, [84–85](#)

magnetic resonance spectroscopy (MRS), [79](#)

positron emission tomography (PET), [77–79](#)

resting-state approaches, [82–84](#)

task-based approaches, [80–82](#)

brain plasticity, [476–479](#)

brain swelling, [479](#)

brain training programs, [537](#)

brain-computer interfaces, [125–126](#), [535](#)
Broca, Paul, [42](#), [224](#)
Broca's aphasia, [45–46](#), [224](#), [225–226](#)
Brodman map, [27](#)
Bucharest Early Intervention Project, [466](#)

callosal apraxia, [134](#)
callosal relay model, [57](#)
categorical spatial relations, [203–207](#)
category specificity. See also [ventral stream](#)
 evidence of, [185–189](#)
 face recognition, [189–190](#)
 recognition of objects other than faces, [190–193](#)
category-specific deficit, [176](#)
central executive, [291](#)
central nervous system. See [nervous system](#)
cerebellar ataxia, [105](#)
cerebellum, [9](#), [104–107](#), See also [nervous system](#)
cerebral achromatopsia, [151](#)
cerebral cortex. See also [nervous system](#)
 association areas, [33–36](#)
 four major lobes of, [14](#)
 primary sensory and motor cortices, [27–33](#)
cerebrocerebellum, [105](#)
cerebrospinal fluid (CSF), [7–8](#)
cholinergic system, [20–21](#), [507](#)
chorea, [110](#), [131](#)
chronic traumatic encephalopathy (CTE), [499](#)
cingulate cortex, [379–381](#), See also [anterior cingulate cortex](#)
clinical neuropsychologists, [3](#)
clinical populations, [70](#)

closed head injury

etiology, [493–494](#)

intervention, [497](#)

neuropsychological consequences, [494–496](#)

sports-related trauma, [497–499](#)

coarticulation, [113](#)

cognitive neuroscience

and morality, [537–540](#)

and the legal system, [530–534](#)

and the marketplace, [536–537](#)

as an interdisciplinary field of research, [69–70](#)

computational and neuroimaging approaches to, [95–97](#)

development of, early 20th century, [43–46](#)

development of, mid-20th century, [46–47](#)

development of, through 1800s, [42–43](#)

impact of social inequality and, [528–530](#)

influence on education policy, [526–528](#)

multi-modal approach to, [92–95](#)

performance optimization, [534–536](#)

public perceptions of, [524–526](#)

research methods, [70–71](#)

the study of, [4](#)

cognitive reappraisal, [383–385](#)

cognitive reserve, [507](#)

cognitive-perspective-taking and empathy, [407–408](#)

cogwheel rigidity, [127](#)

coincidence detectors, [160–161](#)

color constancy, [151](#)

coma, [298](#), [518](#)

compensation, [482](#), [484–485](#), [488](#)

computerized axial tomography (CAT), [62–64](#)

concussion. See [closed head injury](#)
 conduction aphasia, [51](#)
 configural information, [182–183](#)
 confirmation bias, [526](#)
 conformity, [397–399](#)
 conjunctive encoding, [183–185](#)
 conscious recollection, [269–272](#)
 conscious states, [329–330](#)
 constructional apraxia, [134](#)
 constructional praxis, [210–211](#)
 contention scheduling, [334](#)
 contextural fear conditioning, [276](#)
 control group, [70](#)
 coordinate spatial relations, [203–207](#)
 coprolalia, [131](#)
 corpus callosum
 and high-order information transference, [60–62](#)
 function of, [37](#), [53–54](#)
 cortical blindness, [152–153](#)
 cortical dementia. See [frontotemporal dementia](#), [dementia](#), [Alzheimer's disease](#)
 cortical magnification factor, [145](#)
 cosmetic neurology, [536](#)
 countercoup injury, [494](#)
 coup injury, [494](#)
 cranial nerves, [8](#)
 crowding hypothesis, [484](#)
 cueing paradigm, [324](#)
 cytoarchitectonics, [26–27](#)

 Darwin, Charles, [379](#), [385](#)
 deception, [532–533](#)

declarative memory system, [267](#)
decomposition of movement, [105](#)
dedifferentiation, [488](#)
deep brain stimulation, [439–441](#)
deep dyslexia, [244](#)
default network, [317–319](#)
delay aversion, [474](#)
delay discounting, [361](#)
delay line model, [160–161](#)
delayed response task, [288](#)
dementia, [500](#), See also [frontotemporal dementia](#), [Alzheimer's disease](#)
dementia pugilistica, [497–498](#)
dendritic tree, [16](#)
depression
 and the use of transcranial magnetic stimulation (TMS), [91](#)
 effectiveness of St. John's wort on, [25](#)
 genetic predisposition, [441–443](#)
 impact of serotonin levels, [21](#)
 influence of cortical and subcortical regions, [436–437](#)
 influence of frontal lobe, [434–436](#)
 invasive stimulation treatments, [439–441](#)
 noninvasive stimulation treatments, [439](#)
 standard treatments for, [437–439](#)
 symptoms and features, [433–434](#)
depth perception, [202–203](#)
developmental disorders. See [Down syndrome](#), [autism](#), [attention-deficit hyperactivity disorder](#)
developmental milestones, [461](#)
dichotic presentation, [56](#)
diencephalon, [12](#)

diffusion tensor imaging (DTI), [76–77](#)
digit span tasks, [263–264](#)
direct access theory, [57](#)
disconnection syndromes, [51–54](#), [228](#)
disorders of conscious awareness, [518–520](#)
divided attention, [298](#), [313–315](#)
domain-specific neocortical regions and memory, [272–273](#)
dopaminergic system, [22–24](#), [475](#)
dorsal and ventral streams, [220–221](#)
dorsal attention system, [317](#)
dorsal stream, [200](#), [236](#). See also [spatial navigation](#)
double dissociation, [45–46](#), [231–232](#), [242–243](#), [373](#)
Down syndrome, [469](#), [506](#)
dressing apraxia, [134](#)
dual-process models, [283](#)
dysarthria, [105](#)
dyslexia, [243–244](#), [470–472](#)
dysthymia, [433](#)
dystonia, [131](#)

echolalia, [131](#)
edema, [479](#)
egocentric disorientation, [217](#)
egocentric reference frames, [203–204](#)
electroencephalography (EEG), [49–51](#), [85–86](#), [286](#)
emotional contagion and empathy, [407](#)
emotional learning, [371–373](#)
emotions
 experiential aspects, [390–393](#)
 facial expressions, interpretation of, [385–388](#)
 fear and emotional learning, [371–376](#)

fight-or-flight, [369–371](#)
influence of music, [376–377](#)
influence on decision making, [381–383](#)
influence on moral reasoning, [539–540](#)
interoception, [377–379](#)
prosody comprehension, [388–390](#)
regulation of, [383–385](#)
role of anterior cingulate cortex, [379–381](#)
theories on causes of, [368–369](#)

empathy

and autism, [413](#)
facets of, [407–409](#)
relationship to morality, [538](#)

endogenous components, [86](#)

environmental conditions and brain development, [464–468](#)

environmental dependency syndrome, [334–335](#)

enzymatic deactivation, [19](#)

epilepsy

brain mapping treatment, [48](#)
cognitive and psychosocial impairment, [517–518](#)
electroencephalography (EEG), [49](#)
magnetoencephalography (MEG), [88–89](#)
seizures, [48](#), [516–517](#)
therapies, [518](#)

episodic memory, [263](#), [277](#)

error-driven learning, [275](#)

error-related negativity (ERN), [348](#), [380–381](#), [426](#)

ethical review boards, [47](#)

event-related optical signal, [89](#)

event-related potentials, [50–51](#), [86–89](#)

evoked potentials, [86](#)

excitatory postsynaptic potential (EPSP), [16](#)

executive dysfunction. See also [executive function](#)

goal-directed behaviors, [337–341](#)

inhibition, [350–352](#)

response to novelty, [359–360](#)

self-monitoring and evaluation behaviors, [347–350](#)

sequencing and planning behaviors, [341–344](#)

task-setting behaviors, [344–347](#)

executive function. See also [higher-order thinking](#), [goal-directed behaviors](#), [executive dysfunction](#)

abilities associated with, [333–334](#)

creativity and, [358–359](#)

goal-centered processing model, [336](#)

impact of head injury, [496](#)

multi-factor models, [336–337](#)

prefrontal cortex organization, [361–364](#)

Shallice's model, [334–335](#)

Stuss and Benson model, [335–336](#)

unity and diversity model, [336–337](#)

working memory, [364–365](#)

exogenous components, [86](#)

experience-dependent systems, [464](#)

experience-expectant systems, [464](#)

experimental neuropsychologists, [3](#)

explicit/implicit memory systems, [267](#)

extrastriate body area (EBA), [185](#)

eye contact, [403–404](#), [412](#)

eye movement, [116](#), [208–209](#), [412](#)

face recognition, [186–189](#). See also [fusiform face area \(FFA\)](#)

facial asymmetry, [387–388](#)

facial expressions, [385–388](#)
fairness norm, [400–402](#)
false belief task, [404–405](#), [406](#)
fear conditioning, [276](#), [372–373](#)
fear learning, [371–373](#)
feature integration theory, [305](#)
feature-based versus configural coding, [182–185](#)
fetal alcohol spectrum disorders (FASD), [469–470](#)
fight-or-flight, [369–371](#)
figure-ground segregation, [148](#)
form-cue invariance, [179](#)
forward model, [106–107](#)
fragile X syndrome, [457–459](#), [469](#)
frontal eye field (FEF), [110](#), [116](#)
frontotemporal dementia, [508–509](#)
functional brain connectivity, [84–85](#)
functional magnetic resonance imaging (fMRI) procedure, [83–84](#)
fundamental attribution error, [410](#)
fusiform face area (FFA), [185](#), [187](#), [189–190](#). See also [face recognition](#)

Galen (Roman physician), [42](#)
gamma-aminobutyric acid (GABA), [19](#), [109](#), [110](#), [511](#), [518](#)
ganglion cells, [139–140](#)
generalized anxiety disorder, [444](#)
geniculostriate pathway, [142–143](#)
Geschwind, Norman, [51–53](#)
Ginkgo biloba, [24–25](#)
Glasgow Coma Scale (GCS), [494–495](#)
glia, [4](#)
Global Deterioration Scale, [502](#)
glutamate, [19](#)

Go/No-Go task, [350](#)
goal-centered processing model, [336](#)
goal-directed behaviors. See also [executive function](#)
 creation and maintenance of goal, [339–341](#)
 inhibition, [350–352](#)
 initiation of behavior, [337–339](#)
 self-monitoring and evaluation, [347–350](#)
 sequencing and planning, [341–344](#)
 shifting set and modifying strategies, [344–347](#)
Graham v. Florida, [523](#)
Grandin, Temple, [395](#)
grandmother cell theory, [177](#)
graph theory, [85](#)
grapheme-to-phoneme correspondence rules, [243](#)
gray matter
 addiction/substance abuse, [451](#)
 Alzheimer's disease, [504–506](#)
 Down syndrome, [469](#)
 fetal alcohol spectrum disorders (FASD), [470](#)
 schizophrenia, [427](#), [428](#), [431](#)
group studies, [44](#)
guilty knowledge test (GKT), [532–533](#)
gyrus, [13](#)

Halstead-Reitan neuropsychological test battery, [72–73](#)
handedness, [59–60](#)
heading disorientation, [217](#)
Heider-Simmel illusion, [405](#)
Helmholtz, Hermann, [208](#)
hemi-inattention, [35](#)
hemineglect

- clinical features, [319–322](#)
- definition of, [35](#)
- dissociability of reference frames, [205](#)
- symptoms of, [297](#)
- theories on the underlying deficit, [322–325](#)
- treatment, [325](#)
- hemiplegia, [29](#)
- hemispheric independence, [53–54](#)
- hemispheric specialization, [54–59](#)
- hemodynamic response, [80](#)
- herbal supplements, effectiveness of, [24–25](#)
- Heschl's gyrus, [31](#)
- higher-order thinking. See also [executive function](#)
 - abstract and conceptual thinking, [354–356](#)
 - judgement and decision making, [360–361](#)
 - novelty, response to, [359–360](#)
 - rule-governed behavior, [356–358](#)
- hippocampal memory system
 - conscious recollection, [269–272](#)
 - declarative memory system, [267](#)
 - memory storage, [273](#)
 - relational learning, [268–272](#)
 - role in memory retrieval, [282–284](#)
- hippocampus damage
 - skill learning, [264–267](#)
 - temporal effects, [260–263](#)
 - working memory, [263–264](#)
- homeostasis, [11](#)
- homunculus, [48](#)
- Hubel, David, [145](#)

Hughling-Jackson, John, [54](#)

human neuropsychology, [3](#)

Huntington's disease

as a motor disorder, [130–131](#)

cognitive symptoms, [511–513](#)

role of the basal ganglia in, [110](#), [273–274](#)

hyperkinesias, [110](#)

hypothalamus, [11–12](#), [369–371](#)

ideational apraxia, [132](#)

ideomotor apraxia, [133](#)

imitation and simulation, [402–404](#)

inequity aversion, [538](#)

inferior colliculus, [11](#), [157](#), [161](#), [302](#)

informational conformity, [397](#)

inhibition

neural systems activated in, [350–352](#)

of memories, [352–354](#)

inhibitory postsynaptic potential (IPSP), [16](#)

insight, [358](#)

intellectual disability. See [fetal alcohol spectrum disorders \(FASD\)](#), [dyslexia](#), [Down syndrome](#)

intelligence tests, [73–74](#)

intention tremor, [105](#)

interaural intensity difference, [159](#)

interaural time difference, [159](#)

interference solution, [351](#)

interferons, [516](#)

interhemispheric interaction, [60–62](#)

interoception, [349](#), [377–379](#)

intraparietal sulcus, [305–306](#)

inverse problem, [88](#)

inversion effect, [182–183](#)

ion channel, [14–15](#)

ionizing radiation, [62–65](#)

Jacksonian seizure, [48](#)

James, William, [368](#), [377](#)

judgement and decision making, [360–361](#)

justice sensitivity, [538–539](#)

Kandel, Eric, [257](#)

kindling, [518](#)

kinesthetic information, [120](#)

King, Rodney, [530–531](#)

Klüver-Bucy syndrome, [372](#)

Kosslyn, S.M., [195–196](#)

language comprehension, [252–253](#)

language formation, [45–46](#)

language processing

dedicated regions for, [233–234](#)

interaction of brain regions, [236–238](#)

overlap in physiolinguistic systems, [234–236](#)

right-hemisphere contributions to, [250–253](#)

symbol-based languages, [247–250](#)

language, auditory

brain systems, [224–225](#)

double dissociations, [231–232](#)

language processing networks, [232–233](#)

neurological conceptions, [225–228](#)

psycholinguistic systems, [229–238](#)

language, visual, [238–240](#)

late positive potential, [88](#)

lateral geniculate, [303](#)

lateral geniculate nucleus (LGN), [143–144](#)

lateral ventricle, [6](#)

lateralization of function, [56–57](#), [59–60](#)

Lauterbur, Paul, [65](#)

L-dopa, [129](#), [510](#)

left-right determination, [201–202](#)

lesion method

as the basis of cognitive neuroscience, [42](#), [43–44](#)

double dissociation concept, [45–46](#)

limitations of, [46](#)

Levi-Montalcini, Rita, [480](#)

lexical route to reading

brain regions involved in, [245–246](#)

symbol-based languages, [247–249](#)

use with irregular words, [243–244](#)

Lezak, Muriel, [72](#)

limbic system, [12](#)

localization of function, [42](#)

locked-in syndrome, [519](#)

longitudinal fissure, [14](#)

long-term potentiation (LTP), [268](#)

Luria, Alexander, [73](#)

Luria-Nebraska neuropsychological test battery, [73](#)

MacLean, Paul, [369](#)

magnetic resonance spectroscopy (MRS), [79](#)

Mansfield, Paul, [65](#)

Marr, David, [181](#)

mass action, [42](#)

maturational lag hypothesis, [476](#)

McCloskey, Michael, [201](#)

medial temporal lobe (MTL). See also [hippocampal memory system](#)

memory encoding, [278–280](#)

memory formation, [257](#)

spatial navigation, [219–220](#)

medulla, [8–9](#)

memory. See also [working memory](#), [nonhippocampal regions](#), [memory systems](#), [memory retrieval](#), [memory processes](#), [hippocampal memory system](#), [amnesia](#)

impact of serotonin levels, [21–22](#)

role of temporal lobes, [35](#)

memory consolidation

and retrograde amnesia, [262](#)

effect of sleep on, [286–287](#)

role of hippocampus in, [280–282](#)

memory enhancement effect, [374](#)

memory formation, [44](#)

memory processes

consolidation and storage, [280–282](#)

encoding, [278–280](#)

memory reactivation, [286](#)

memory retrieval

effect of sleep on, [286–287](#)

role of hippocampus in, [282–284](#)

role of parietal cortex in, [285](#)

role of prefrontal cortex in, [284–285](#)

memory systems, [292–293](#)

mental imagery, [195–196](#)

mentalizing, [402–403](#), [404–407](#), [412–413](#)

mesocortical dopaminergic subsystem, [23](#)

mesolimbic dopaminergic subsystem, [23](#)

method of converging operations, [69–70](#)
 midbrain, [10](#)
 mild cognitive impairment, [502](#), [507](#)
 mild traumatic brain injury, [496](#)
 Milner, Brenda, [43](#), [257](#)
 mimicry. See [imitation and simulation](#)
 Mind-in-the-Eyes task, [405](#)
 Mini Mental State Exam, [500](#)
 minimal groups design, [415–416](#)
 mirror neurons, [116–118](#), [403–404](#)
 mirror reading task, [264](#)
 mirror tracing task, [264](#)
 mismatch negativity, [87](#)
 mixed-variety dementias. See [vascular dementia](#), [multiple sclerosis \(MS\)](#), [epilepsy](#),
[disorders of conscious awareness](#)
 modules, [42](#)
 morality, [537–540](#)
 Morris water maze, [265](#)
 motion parallax, [203](#)
 motion perception, [207–209](#)
 motor control
 anterior cingulate cortex, [118–119](#)
 basal ganglia, [107–110](#)
 cerebellum, [104–107](#)
 impact of damage to basal ganglia, [12–14](#)
 impact of nigrostriatal dopaminergic subsystem, [22](#)
 influence of cerebellum, [9](#)
 mechanisms of, [102–103](#)
 medial prefrontal cortex, [306–307](#)
 motor tracts, [102](#)
 parietal lobe, [123](#)

primary motor cortex, [28–29](#), [111–112](#)
right inferior frontal cortex, [118–119](#)
motor cortex, [28–29](#), [480–481](#)
motor disorders, cortical. See [apraxia](#)
motor disorders, subcortical
 Huntington's disease, [130–131](#)
 Parkinson's disease, [127–129](#)
 Tourette's syndrome, [131–132](#)
motor plans
 concept of, [112–114](#)
 role of the supplementary motor complex in, [114–118](#)
motor strip, [28–29](#), [48](#)
motor system, integration of, [123–125](#)
motor tics. See [Tourette's syndrome](#)
motor tracts, [102](#)
multiple sclerosis (MS), [26](#), [514–516](#)
multiple trace theory, [281–282](#)
multiple-case-studies, [44–45](#)
multi-tasking, [313–315](#)
multi-voxel pattern analysis (MVPA), [81–82](#), [291](#)
music, [249–250](#)
myelination, [25–26](#), [459–460](#), [514](#)

N-acetylaspartate (NAA), [79](#)
National Adult Reading Test, [74](#)
N-back task, [291](#)
nerve growth factor (NGF), [479](#)
nervous system. See also [spinal cord](#), [pons](#), [midbrain](#), [medulla](#), [limbic system](#),
 [hypothalamus](#), [cerebral cortex](#), [cerebellum](#), [basal ganglia](#)
 classes of cells, [4–5](#)
 electrochemical signaling, [14–19](#)

impact of myelin on speed of electrical signals, [25–26](#)
 network analysis, [85](#)
 neurodevelopmental hypothesis, [431–432](#)
 neurofibrillary tangles, [503](#)
 neurologically intact populations, [70–71](#)
 neuro-marketing, [536–537](#)
 neurons, [4](#), [6](#), [9](#), [14–19](#)
 neuropsychological assessments
 fixed test batteries, [72–73](#)
 flexible test batteries, [73](#)
 use of NIH Toolbox, [74](#)
 neurotransmission, [18–19](#)
 neurotransmitter agonists, [19](#)
 neurotransmitter antagonists, [19](#)
 neurotransmitter binding, [78](#)
 neurotransmitter systems. See [serotonergic system](#), [noradrenergic system](#),
 [dopaminergic system](#), [cholinergic system](#)
 nigrostriatal dopaminergic subsystem, [22](#)
 nodes of Ranvier, [26](#)
 nonhippocampal regions
 amygdala, [275–277](#)
 anterior temporal regions, [277–278](#)
 basal ganglia, [273–275](#)
 involved in memory, [272–273](#)
 non-local binding, [183–185](#)
 noradrenaline, [22](#)
 noradrenergic system, [22](#), [299](#)
 normative conformity, [397](#)
 novelty, response to, [359–360](#)
 numerical cognition, [215–216](#)

object recognition, [193–194](#). See also [ventral stream](#), [object recognition, visual](#), [agnosias, visual](#), [agnosias, tactile](#), [agnosias, auditory](#)

object recognition, visual. See also [ventral stream](#), [agnosias, visual](#)
and the ventral stream, [169–171](#)
feature-based versus configural coding, [182–185](#)
invariance, problem of, [179–182](#)
sparse versus population coding for, [176–179](#)

object-based response selection, [310–311](#)

obsessive-compulsive disorder (OCD), [444](#), [448–449](#)

occipital face area (OFA), [187](#)

oddball paradigm, [87](#)

Ogden, Jenni, [400](#)

olfactory bulbs, [32](#)

olfactory cortex, [32](#)

oligodendrocytes, [25](#)

optic ataxia, [211–212](#)

optic chiasm, [143](#)

optic nerve, [140](#)

optical imaging, [89–90](#)

optimal feedback control, [123](#)

orthography, [244](#), [246](#)

panic disorder, [444](#)

Papez, James W., [369](#)

parahippocampal place area (PPA), [185](#), [217–218](#)

parallel processing, [138](#)

paraphasias, [227](#)

parietal lobe
apraxia, [35](#)
role in attention, selective, [303–306](#)
role in motor control, [123](#)

- role in spatial cognition, [204–205](#)
- parietal reach region (PPR), [212](#)
- Parkinson's disease
 - attributes of, [101](#)
 - cognitive symptoms, [509–511](#)
 - etiology of, [127](#)
 - role of the basal ganglia in, [110](#), [128–129](#), [273–274](#)
 - symptoms of, [127–128](#)
 - therapies for, [129](#)
- pattern completion, [282](#)
- pattern separation, [279](#)
- Pavlovian fear conditioning, [276](#)
- Penfield, Wilder, [48](#)
- perception, [137](#)
- perceptual constancy, [179](#)
- perceptual filling-in of the blind spot, [149](#)
- peripheral nervous system, [7–8](#)
- perservation, [335](#)
- phantom limb sensations, [29](#), [477](#)
- phase coupling, [85–86](#)
- phobias, [444](#)
- phoneme, [229](#)
- phonological awareness, [471](#)
- phonological dyslexia, [243](#)
- phonological route to reading
 - association of print with meaning, [243–244](#)
 - brain regions involved in, [245–246](#)
 - symbol-based languages, [247–249](#)
- phonology, [229–230](#)
- photoreceptors, [138–139](#)

planum temporale, [59](#), [163](#)
pons, [10–11](#)
population coding, [176–179](#)
position-invariant recognition, [180](#)
postsynaptic potentials, [14–19](#)
posttraumatic amnesia, [495](#)
posttraumatic stress disorder (PTSD), [444](#)
poverty, impact on cognitive function, [528–530](#)
praxis, [134](#)
premorbid functioning, [74](#)
premotor regions, [116–118](#)
primary motor cortex, [111–112](#)
primary sensory and motor cortices, [28–29](#)
primary visual cortex, [144–149](#)
priming effects, [328–329](#)
priority maps, [305–306](#)
procedural memory system, [267](#)
propositional knowledge, [195–196](#)
proprioception, [29](#), [120](#)
pro-social behavior and empathy, [409](#)
prosody, [251–252](#), [388–390](#)
prosopagnosia, [174–175](#), [186–187](#)
prosthetic limb activation, [125–126](#)
psychic blindness, [372](#)
psychological inertia, [337](#)
psychopathology. See [substance use disorders](#), [schizophrenia](#), [depression](#), [anxiety disorders](#)
pulvinar, [303](#)

qualitative neuropsychological assessments, [74](#)

racial biases, neural basis for, [417](#)
receptive field, [170](#)
receptive fields, [140–141](#)
receptors, [15](#), [22](#)
reinforcement contingency, [382](#)
relational learning, [269](#)
relay centers, [12](#)
repetitive transcranial magnetic stimulation (rTMS), [439](#)
response inhibition, [118–119](#)
response selection, [307](#), [309–311](#)
resting potential, [14](#)
resting-state studies, [82–84](#)
reticular activating system, [9](#)
retina
 cell components of, [138–141](#)
 coding of spatial dimensions and, [201–202](#)
 pathways to the brain and the, [141–143](#)
retinotopic mapping, [143–144](#), [150–151](#), [199](#)
retrograde amnesia, [261–263](#), [280–281](#)
retrosplenial complex, [218–219](#)
reuptake, [18](#)
reversal learning, [382](#)
reward pathways, [375–376](#), [449–452](#)
Rey-Osterrieth Complex Figure, [210](#)
rhodopsin, [138](#)
Ribot, Theodule, [262](#)
rods and cones, [138–139](#)
Rolandic fissure, [13–14](#)
route-based versus cognitive map strategies, [216](#)
rule-governed behavior, [356–358](#)

S allele, [441–443](#)

saccades, [302](#)

Sacks, Oliver, [395](#)

schizophrenia

abnormal functional connectivity and, [429–430](#)

causes of, [430–432](#)

impact of dopaminergic receptors on, [22](#)

implications for treatment, [432–433](#)

influence of frontal lobe, [426–427](#)

influence of temporal lobe, [427–429](#)

symptoms and features, [424–426](#)

self perception, [409–411](#)

self-monitoring and evaluation, [347–350](#)

self-ordered pointing task, [341–342](#)

semantic memory, [277–278](#)

semantics, [231–238](#), [252](#)

sense of smell, [32](#)

sense of taste, [32](#)

sense of touch, [29](#)

sensory deprivation, [484–485](#)

sensory gating, [427](#)

sensory processing and hemineglect, [320–322](#)

sensory-motor transformations

constructional praxis, [210–211](#)

neural mechanisms of, [212–214](#)

optic ataxia, [211–212](#)

sequencing and planning behaviors, [341–344](#)

serotonergic system, [21–22](#)

serotonin transporter gene, [441](#)

serotonin-selective reuptake inhibitors (SSRIs), [21](#), [438](#)

Shallice's executive function model, [334–335](#)
short-term memory. See [working memory](#)
signal averaging, [50–51](#)
single photon emission computed tomography (SPECT), [78](#)
single-case studies, [44](#)
single-cell recordings, [47](#), [186–187](#)
social brain hypothesis, [395–396](#)
social cognition. See also [social groups](#)
 autism, [411–413](#)
 conformity, [397–399](#)
 empathy, [407–409](#)
 imitation and simulation, [402–404](#)
 mentalizing, [402–403](#), [404–407](#)
 self-perception, [409–411](#)
 social norm compliance, [399–402](#)
social exclusion, [414](#)
social groups. See also [social cognition](#)
 and social biases, [416–419](#)
 in-group and out-group categorization, [415–416](#)
social influence. See [social norm compliance](#), [conformity](#)
social norm compliance, [399–402](#)
socio-economic status, impact on cognitive function, [528–530](#)
somatosensory cortex, [29](#), [476–479](#)
source memory, [487](#)
space-based response selection, [309](#)
sparse coding, [176–179](#)
spatial cognition. See also [spatial navigation](#), [spatial frames of reference](#)
 coding for three dimensions, [201–203](#)
 motion perception, [207–209](#)
 sensory-motor transformations and, [210–214](#)

spatial frames of reference, [203–207](#)

spatial navigation. See also [spatial cognition](#), [dorsal stream](#)

 navigational skills, [153–155](#), [216–217](#)

 role of brainstem, [159–161](#)

 role of medial temporal lobe (MTL) in, [219–220](#)

 role of parahippocampal place area in, [217–218](#)

 role of retrosplenial complex in, [218–219](#)

speech formation. See [language formation](#), [language, visual](#), [language, auditory](#)

Sperry, Roger, [53](#), [54](#)

spinal column, [7](#)

spinal cord, [7–9](#). See also [nervous system](#)

spinocerebellum, [104](#)

split-brain studies, [53–56](#)

sports-related head injuries, [497–499](#)

St. John's wort, [25](#)

state estimation, [122](#)

Steele, Claude, [417](#)

stereotype threat, [417–419](#)

Stroop task, [118](#)

Stuss and Benson executive function model, [335–336](#)

subcortical dementias. See [Parkinson's disease](#), [Huntington's disease](#)

subcortical systems, [12–14](#)

substance use disorders, [449–452](#)

superior olive, [10](#)

supervisory attentional system, [334](#)

supplementary motor area, [102](#)

supplementary motor complex, [114–118](#)

supranuclear palsy, [302](#)

surface dyslexia, [243](#)

Sylvian fissure, [13](#)

synaptic vesicles, [15–17](#)
synaptogenesis, [457–459](#)
syntax, [230–231](#)

tactile object recognition, [193–194](#)
tactile stimulation, [29](#)
task/set shifting, [345–347](#)
task-based studies, [80–82](#)
tectopulvinar pathway, [141–142](#)
telegraphic speech, [226](#)
theory of mind. See [mentalizing](#)
Think/No-Think task, [352](#)
time-frequency analysis, [85](#)
tonotopic map, [157](#), [162](#)
tonotopic organization, [31](#)
top-down attentional selection, [300](#), [312–313](#)
Tourette's syndrome, [131–132](#)
Tower of London task, [343](#)
transcranial direct current stimulation (tDCS), [91–92](#)
transcranial magnetic stimulation (TMS), [90–91](#)
transformation hypothesis, [281–282](#)
transneuronal degeneration, [479](#)
traumatic brain injury (TBI), [493–494](#)
tremors, [127](#)
true recovery, [482](#)

ultimatum game, [400–402](#)
unity and diversity executive function model, [336–337](#)
unresponsive wakefulness syndrome (UWS), [519–520](#)

vagus nerve stimulation, [441](#)

valence-arousal model, [391–393](#)
vascular dementia, [513–514](#)
vegetative state, [519](#)
ventral attention system, [317](#)
ventral stream. See also [object recognition, visual](#), [object recognition, category specificity](#), [agnosias, visual](#)
 deficits in, [171](#), [175–176](#)
 neural characteristics, [169–171](#)
 object recognition, [153–155](#)
 role in language processing, [237](#)
ventricular enlargement, [424](#)
vertebrae, [7–9](#)
vestibulocerebellum, [104](#)
viewpoint dependence, [181–182](#)
viewpoint invariance, [180–182](#)
vigilance, [300](#)
vision, color, [151–152](#), [171](#)
visual contrast, [140–141](#)
visual item recognition, [35–36](#)
visual language processing (reading)
 brain activity in late learners, [247](#)
 brain region activity and, [245–246](#)
 cognitive processes of, [243–244](#)
 dyslexia, [470–472](#)
 processing of visual word forms, [244–245](#)
visual pathways, [152–155](#)
visual systems, [29–31](#)
visual word form area (VWFA), [185](#), [190–191](#), [245](#)
Vogel, Philip, [53–54](#)
von Economo neurons, [379](#)
voxels, [80](#)

Wada technique, [54](#), [224](#)
waveform components, [50–51](#)
Wechsler intelligence tests, [73](#)
Wernicke, Karl, [226](#)
Wernicke's aphasia, [45–46](#), [226–227](#)
white matter tracts
 and brain conductivity, [36–37](#)
 and disconnection syndromes, [51–53](#)
 as a measurement of brain connectivity, [76–77](#)
 as basis for language processing, [236](#)
 effects of aging on integrity of, [488](#)
 impact on reading skill, [461](#)
Wiesel, Torsten, [145](#)
Wisconsin Card Sorting Test (WCST), [344–347](#)
within-hemisphere processing, [61–62](#)
word-stem completion task, [265](#)
working memory
 and amnesia, [263–264](#)
 deficit symptoms, [288](#)
 executive function, [364–365](#)
 posterior cortex, [289–291](#)
 prefrontal cortex, [288–289](#), [291](#)
writing, [244](#)

Endpapers

Methods Used in Cognitive Neuroscience and Neuropsychology

METHODS OF ASSESSING BRAIN ANATOMY

| | Information Provided | Spatial Resolution | Temporal Resolution |
|-------------------------------------|---|--------------------|---------------------|
| CAT (computerized axial tomography) | Anatomical image of brain density | 0.5–1.0 cm | Not available |
| MRI (magnetic resonance imaging) | Anatomical image of the distribution of a certain substance, such as water or fat | 1 mm | Not available |

METHODS OF ASSESSING BRAIN PHYSIOLOGY

Functional Brain Imaging

| | Information Provided | Spatial Resolution | Temporal Resolution |
|------------------------------------|---|--------------------|---------------------|
| PET (positron emission tomography) | Functional image of physiological activity for various substances, including glucose, oxygen, and neurotransmitters | 5–10 mm | 40 seconds–1 hour |

| | | | |
|-----------------------------|--|--------|--------------|
| fMRI (functional MRI) | Functional image of relative blood oxygenation or blood flow | 3–7 mm | .5–2 seconds |
|-----------------------------|--|--------|--------------|

Methods of Assessing Electromagnetic Activity

| | Information Provided | Spatial Resolution | Temporal Resolution |
|-----------------------------------|--|-----------------------|--|
| Single Cell | Electrical signal that provides information about the firing rate of a cell | 1/100th mm | 1–2 milliseconds (1 thousandth of a second) |
| EEG (electroencephalography) | Electrical signal that provides information about the summed postsynaptic dendritic activity (typically provided in frequency, Hz) | Poor | 1–2 milliseconds |
| ERP (event-related potentials) | Electrical signal that provides a record of the averaged electrical activity that is time- locked to an event | Poor | 1–2 milliseconds |
| MEG (magnetoencephalography) | Magnetic potentials that provide information derived from the electrical activity of neurons | 5 mm | 1–2 milliseconds |

Optical Imaging

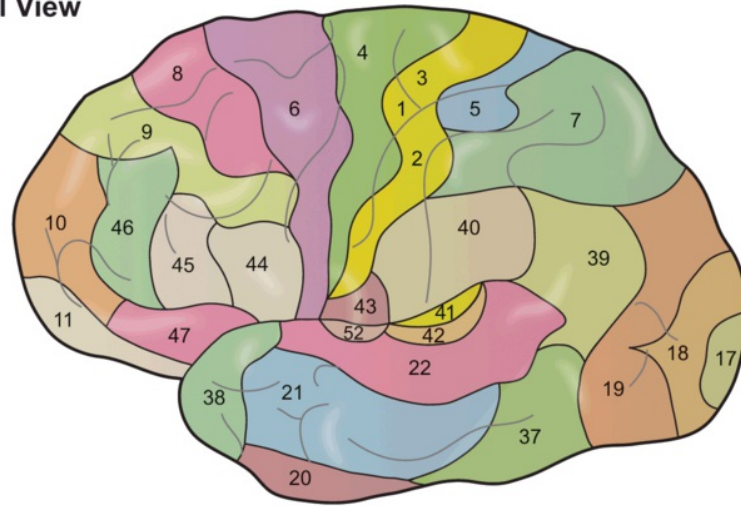
| | Information Provided | Spatial Resolution | Temporal Resolution |
|---|---|---------------------------|----------------------------|
| Slow Signal (metabolic) | Laser light provides information on the concentration of oxygenated and deoxygenated blood | 1–5 mm | 1–2 seconds |
| Fast Signal-EROS (event-related optical signal) | Laser light provides information on the deformation of neurons that accompanies neuronal firing | 1–5 mm | 1–2 milliseconds |

METHODS OF MODULATING BRAIN ACTIVITY

| | Means of Modulating Activity | Spatial Resolution | Temporal Resolution |
|--|---|---------------------------------------|---------------------------------------|
| TMS (transcranial magnetic stimulation) | Pulsed magnetic field induces an electric field causing neurons to fire in a random pattern | Currently ambiguous probably 10–15 mm | Currently ambiguous probably 20–50 ms |
| tDCS (transcranial direct current stimulation) | Constant low direct current stimulation modulates neuronal firing | Poor | 100 milliseconds |

Brodmann Areas

(A) Lateral View



(B) Medial View

